

# Effect of dexmedetomidine on hemodynamic responses during the propofol induction period, skull-pin application and skin incision in patients under going craniotomy

Ananchanok Saringcarinkul, Yodying Punjasawadwong, Natta Kongtonkul, and Kornkamol Werawong

Department of Anesthesiology, Faculty of Medicine, Chiang Mai University

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**Objectives** The authors of this study hypothesized that dexmedetomidine (DEX) would attenuate hemodynamic changes during the propofol induction period, skull-pin application and skin incision in supratentorial craniotomy, when compared with fentanyl.

**Methods** Thirty patients (18-70 years), who were scheduled for elective intracranial surgery, received infusions of DEX at 1 µg/kg (group D) or fentanyl at 2 µg/kg (group F) before propofol-based anesthesia. Propofol was started at 3.0 µg/mL on a target control syringe pump and titrated to maintain a similar level of sedation by using the Bispectral index in both groups. The hemodynamic variables were recorded continuously and analyzed for the results.

**Results** Overall, the arterial pressures [systolic (Ps), diastolic (Pd) and mean arterial pressure (MAP)] increased after receiving infusion of DEX at 1 µg/kg and were higher than those in patients receiving fentanyl for the whole period of the study. Ps, Pd, and MAP in group F decreased after 2 µg/kg of fentanyl infusion and decreased further through propofol induction, and then increased by responding to endotracheal intubation. Pd and MAP increased in both groups after skull pin fixation, but with no significant difference from the pre-skull pin fixation value in each group. Ps, Pd and MAP in both groups did not change much after skin incision, when compared to pre-skin incision values. The induction and total doses of propofol in group D were smaller than those in group F, and group D required less fentanyl intraoperatively when compared to group F, but with no statistical significance.

**Conclusion** DEX at 1 µg/kg was no more effective than fentanyl at 2 µg/kg on blunting hemodynamic responses to endotracheal intubation, skull-pin fixation, and skin incision in craniotomy patients, even though it helped to stabilize the hemodynamic during propofol induction. **Chiang Mai Medical Journal 2015;54(1):1-7.**

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**Keywords:** dexmedetomidine, hemodynamic response, skull pin application, craniotomy

## Background

Dexmedetomidine (DEX) is a potent and highly selective alpha 2-adrenoreceptor agonist currently utilized for continuous infusion for sedation/analgesia in the intensive care unit. In addition, it possesses sympatholytic and antinociceptive effects that allow hemodynamic stability during surgical stimulation, reduces anesthetic and opioid requirements, and causes sedation and analgesia<sup>[1]</sup>. There have been several studies of DEX administration as an adjunct of general anesthesia in different sorts of operations. However, few studies have focused on DEX during neuroanesthetic induction; therefore, its use has not been widespread. Relative or absolute hypotension can occur during many neurological procedures; either as a side effect of drugs used in the perioperative period (e.g. anesthesia induction agents, excessive beta-adrenergic-blocker administration) or as a result of hypovolemia, due to bleeding or diuretic use. Maintenance of adequate cerebral perfusion is critically important<sup>[2]</sup>. However, hypertension is common during intracranial procedures, and 60% to 90% of patients undergoing craniotomy require treatment with antihypertensive medications<sup>[3-5]</sup>. Pressures above the upper cerebral autoregulation threshold may result in breakthrough edema, hemorrhage, seizures, and posterior leukoencephalopathy (e.g. hypertensive encephalopathy)<sup>[6]</sup>. Therefore, the authors conducted this study to determine the effect of DEX on hemodynamic responses during induction, skull-pin application and skin incision in neurosurgical patients undergoing craniotomy, compared to that of fentanyl, which is a common analgesic agent used in attenuating pain perception and hemodynamic responses during neurosurgical anesthesia. The aim of the study was to determine if DEX was more beneficial than fentanyl in stabilizing hemodynamics during anesthetic induction with propofol, and perioperative noxious stimuli.

## Methods

This prospective, randomized-control study was approved by the institutional review board of the Fac-

ulty of Medicine, Chiang Mai University, with written informed consent from the patients. The authors enrolled 30 patients, aged 18-70 years, with 15 patients per group, due to this research being a pilot study. The patients had an ASA physical status of I to III, and were scheduled for elective supratentorial craniotomy with attachment of a pin head-holder at Maharaj Nakorn Chiang Mai Hospital, Thailand, between January and December, 2010. The exclusion criteria comprised a preoperative decrease in the level of consciousness (Glasgow Coma Scale <14), conditions of bradycardia (heart rate <60 /min), or heart block, and complication occurring during surgery such as unanticipated brain swelling, injury to the cranial nerves, massive blood loss or unstable vital signs, difficulty in communication, and no plan to extubate. After monitoring (NIBP, EKG, pulse oximeter and arterial line), the patients were allocated randomly into two groups using a computer generated random number chart. Group D received intravenous infusion by 10 mL of DEX (1 µg/kg) over 10 minutes followed by 0.6 µg/kg/hr (6 mL/hr), while group F received 10 ml of fentanyl (2 µg/kg), prepared by a nurse anesthetist, who did not participate in the anesthetic care of each patient. Therefore, the anesthesiologist, neurosurgeon, and patient were blinded to the drug being administered. After 10 minutes of DEX or fentanyl, propofol was started at 3.0 µg/mL on a target-controlled infusion (TCI) syringe pump, and titrated to maintain a similar level of hypnosis in both groups using the Bispectral index (BIS) at a range of 40-60. Rocuronium was given at a dose of 0.9 mg/kg. Then, the patients were ventilated for 5 minutes to enable intubation. The propofol dose for induction and duration of anesthetic induction (from the start of propofol infusion to the patient falling asleep and the BIS becoming less than 60) were recorded. Hemodynamic variables, SpO<sub>2</sub> and BIS were measured continuously during the induction period, skull pin application and skin incision. Patients in both groups received a dose of fentanyl at 2 µg/kg five minutes before skin incision. Anesthesia was maintained with air in oxygen (50%: 50%) and propofol infusion at a TCI dose of 3 µg/min. However, this could be changed to maintain a depth of anesthesia at the BIS of range 40-60; and fentanyl given at 0.5 µg/kg was titrated increasingly in order to maintain blood pressure and heart rate within 30% of the baseline value. DEX or saline was infused at the rate of 2 mL/hr from the time of skin incision to completion of the operation. Anesthetic management depended on the judgment of the attending anesthesiologist, and was not influenced or intentionally altered as a result of participating in this study. Plans were made to extubate all patients

and transfer them to the intensive care unit (ICU) for at least 24 hours monitoring.

All patients were recorded and analyzed for systolic pressure (Ps), diastolic pressure (Pd) and mean arterial pressure (MAP) by measuring as direct blood pressure and monitoring through an arterial catheter. The heart rate (HR) was taken at 8 time points: 1) T1 at base line, 2) T2 10 minutes after DEX or fentanyl infusion, 3) T3 3 minutes after propofol induction, 4) T4 3 minutes after endotracheal intubation, 5) T5 before skull pin fixation, 6) T6 3 minutes after skull pin fixation, 7) T7 before skin incision, 8) T8 3 minutes after skin incision. The Statistical Package for Social Science program (SPSS for Windows, version 16.0) was used for analyzing the data. Statistical significance was determined at a *p*-value of less than 0.05. The primary outcome of this study was the effect of DEX and fentanyl on hemodynamic responses (arterial pressure and heart rate) during propofol induction, skull-pin application and skin incision. The secondary outcome measured the effect of DEX on anesthetic requirement (induction dose of propofol, total dose of propofol and fentanyl). Discrete categorical data were presented as frequency (percent) and compared between groups by the chi-square or Fisher's exact test. Continuous data such as arterial pressure and heart rate, and propofol and fentanyl doses, were presented as mean±SD, and compared between groups by using the independent t-test or Mann Whitney U test; while repeated-measures ANOVA was used for within-group comparisons.

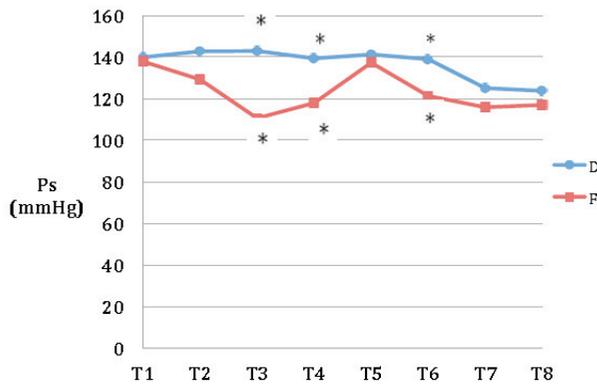
## Results

Thirty patients were enrolled in this study, and divided into 15 per group. There were no significant differences between the groups in demographic characteristics, including age, sex, body weight, and duration of surgery and anesthesia (Table 1). Time to eyelash reflex loss and BIS 60 after induction, propofol induction dose and amount of propofol by intubation, total amount of propofol and fentanyl, and volume of the research drug are shown in Table 1, which indicated no significant differences between the groups.

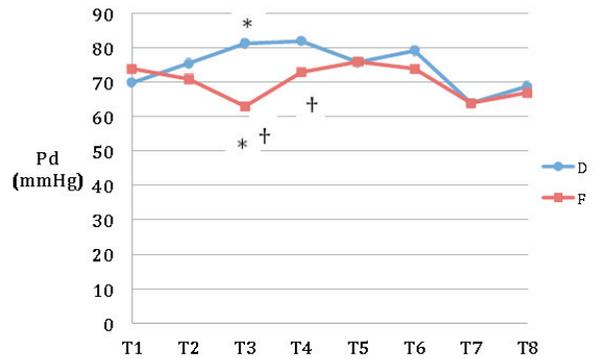
Overall, the increased arterial pressure (Ps, Pd and MAP) in group D patients after receiving DEX at 1 µg/kg infusion was higher than that of the patients in group F during the entire period of this study. Whereas the Ps, Pd, and MAP of patients in group F decreased after 2 µg/kg of fentanyl, decreased further with propofol induction (T3), and then increased when responding to endotracheal intubation (T4). However, there were only 3 time points (T3, T4 and T6) when the Ps of group D was significantly higher than that of group F (142.93±17.93 vs 110.55±21.50, 139.33±16.93 vs 117.82±18.09, and 138.93±19.83 vs 121.36±19.04 mmHg,

**Table 1.** Demographic and intraoperative data

	DEX group	Fentanyl group (n=15)	<i>p</i> -value
Age (year)	48.4±14.9	47.7±12.7	0.886
Gender (male/female)	7 (47%)/8 (53%)	7 (47%)/8(53%)	1.000
Weight (kg)	56.1±11.0	60.3±9.5	0.271
ASA physical status (I/II/III)	4(27%)/ 9(60%)/2(13%)	2(13%)/12(80%)/1(7%)	0.490
Premedication (midazolam/ diazepam/lorazepam)	3(20%)/ 2(13%)/10(67%)	6 (40%)/2(13%)/7(47%)	0.465
Diagnosis (brain tumor/other)	15(100%)/0	14(93%)/1(7%)	1.000
Propofol induction dose (mg)	57.0±11.4	60.0±24.0	0.719
Time to eyelash reflex loss (sec)	101.1±95.8	77.5±60.6	0.433
Time to BIS 60 after induction (min)	2.6±2.2	3.5±2.7	0.323
Propofol dose by intubation time (mg)	126.3±45.1	102.6±33.2	0.140
Total dose of propofol (mg)	2202.1±886.1	1785.5±559.3	0.135
Total dose of fentanyl (µg)	111.4±58.2	204.4±95.4	0.349
Total volume of study drug (mL)	23.3±3.1	23.8±4.8	0.755
Duration of surgery (min)	225.7±83.7	241.2±124.2	0.691
Duration of anesthesia (min)	302.1±94.7	310.7±129.8	0.837



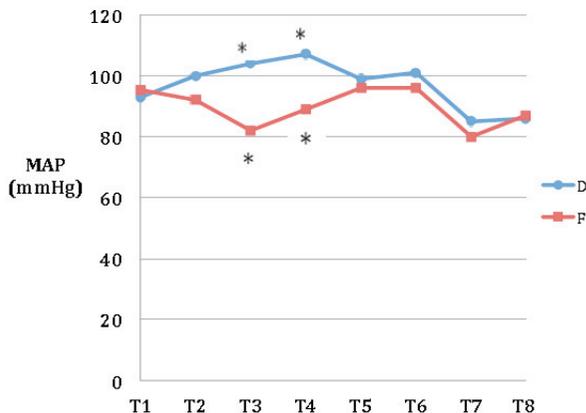
**Figure 1.** Systolic pressure at different time points  
 D= dexmedetomidine group, F= fentanyl group  
 T1= Ps at baseline, T2= Ps before anesthetic induction, T3=Ps after anesthetic induction, T4=Ps after endotracheal intubation, T5=Ps before skull pin fixation, T6=Ps after skull pin fixation, T7=Ps before skin incision, T8=Ps after post skin incision



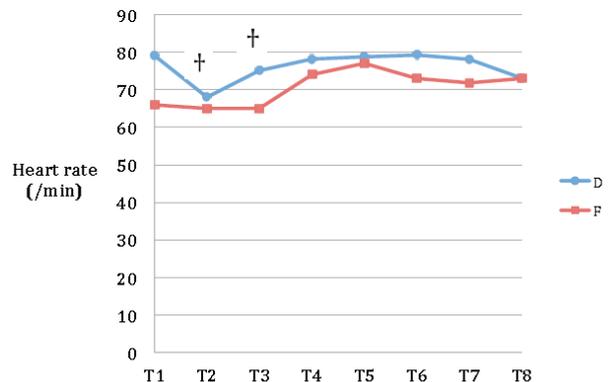
**Fig 2.** Diastolic pressure at different time points

†Statistically significant differences within a group compared with the previous parameter value of that group ( $p < 0.05$ )

\*Statistically significant differences between 2 groups ( $p < 0.05$ )



**Figure 3.** Mean arterial pressure at different time points



**Figure 4.** Heart rate at different time points.

$p = 0.000, 0.005$  and  $0.033$ , respectively). The MAP of group D was higher than that of group F at two time points (T3 and T4:  $103.80 \pm 13.50$  vs  $82.18 \pm 12.77$  and  $106.07 \pm 12.89$  vs  $89.18 \pm 18.52$ ,  $p = 0.000$  and  $0.007$ , respectively). The Pd of group D was significantly higher than that in group F ( $81.27 \pm 12.27$  vs  $63.17 \pm 12.72$  mmHg,  $p = 0.001$ ) only after propofol induction (T3). After skull pin fixation (T6), the Pd and MAP in both groups increased, but with

no significant difference from the pre-skull pin fixation value (T5) in each group. The Ps, Pd and MAP in both groups did not change much between pre-skin incision value (T7) and post skin incision (T8).

The heart rate of patients in group D decreased significantly from baseline (T1) [ $79.67 \pm 20.27$  to  $67.60 \pm 14.90$  ( $p = 0.008$ )] after DEX infusion. After that, the heart rate in group D increased significantly after 3 minutes of propofol induction

(T3) ( $p = 0.041$ ), then slightly increased after endotracheal intubation (T4), before becoming quite stable. The heart rate of patients in group F did not change significantly from baseline after receiving fentanyl (T2) or post propofol infusion (T3), but it increased after endotracheal intubation (T5) before becoming quite stable after skull pin application (T6) and skin incision (T8).

## Discussion

DEX has a sympatholytic effect and causes a significant reduction in circulating catecholamines, modest reduction in blood pressure, and modest reduction in heart rate<sup>[7,8]</sup>. Kuni-sawa T, *et al*<sup>[9]</sup> evaluated the effect of DEX combined with fentanyl on hemodynamics and concluded that DEX administration during anesthetic induction may be useful because it suppresses the decrease in blood pressure during anesthetic induction and blunts the cardiovascular response to tracheal intubation. The authors of this study found that arterial blood pressure increased from baseline after intravenous infusion of DEX at 1  $\mu\text{g}/\text{kg}$  loading dose through the time of anesthetic induction, which therefore helped to attenuate the effect of propofol by decreasing blood pressure during induction, as stated in the study of Kuni-sawa T. Whereas, blood pressure decreased in patients receiving fentanyl at 2  $\mu\text{g}/\text{kg}$  and decreased further after propofol induction. However, it seemed that DEX did not help in reducing the induction and total doses of propofol, probably due to the small sample size. This was in contrast to the study of Basar H<sup>[10]</sup> because a single dose of DEX at 0.5  $\mu\text{g}/\text{kg}$ , given before induction of anesthesia, decreased thiopental requirements without serious hemodynamic effects or any effect on recovery time. Compared with fentanyl, DEX intubated the trachea faster without respiratory depression in the study of Tanskanen PE<sup>[11]</sup> and increased perioperative hemodynamic stability in patients undergoing brain tumor surgery.

Substantially acute hypertension and possible increase in cerebral blood flow can result from insertion of a skull-pin head holder

during craniotomy. These hemodynamic responses may lead to brain edema, increased intracranial pressure, or intracranial hemorrhage<sup>[12]</sup>. Uyar AS, *et al*<sup>[13]</sup> conducted a study of a single bolus dose of DEX at 1  $\mu\text{g}/\text{kg}$  before induction with thiopental, and found that it helped attenuate hemodynamic and neuroendocranial responses to skull-pin in patients undergoing craniotomy. In this study, the effect of DEX on sympatholytic response to noxious stimuli, such as endotracheal intubation and skull pin application was not so obvious, because patients in group D did not receive fentanyl until just before skin incision, which is why the result in this study was different from that of Uyar AS. Nevertheless, the blood pressure and heart rate did not increase significantly compared to baseline values. Therefore, the authors of this study assumed that DEX was still useful in this circumstance. The study of Bekker A, *et al*<sup>[3]</sup> showed that intraoperative DEX infusion was effective for perioperatively blunting the increase in systolic blood pressure. Perhaps, loading the DEX dose of 1  $\mu\text{g}/\text{kg}$  started after tracheal intubation and before skull-pin fixation, straight after a stimulus, and was followed by another stimulus; and that is why the use of DEX did not increase the incidence of hypotension or bradycardia. However, 2 patients in this study had bradycardia in 5 minutes after receiving DEX infusion 10 minutes before propofol induction; and the authors explained that starting DEX at the time of no stimuli brought on an incidence of bradycardia.

Ilhan O, *et al*<sup>[14]</sup> found that DEX controlled the hemodynamic changes perioperatively better than fentanyl. It seems that DEX is safer and more effective in controlling hemodynamic changes during surgical stimulation than the standard agents used in neuroanesthesia. Whereas, a preliminary study conducted by Sturaitis M, *et al*<sup>[15]</sup> on the perioperative use of DEX in patients undergoing craniotomy for brain tumor under general anesthesia, indicated that intraoperative administration of DEX is opioid-sparing, results in less need for antihypertensive medication, and may offer greater hemodynamic stability in incision and emergence. However,

this study was concerned mainly with the hemodynamic responses at the beginning of anesthesia and surgery. Also, the authors did not find any effect of DEX in reducing total opioid requirement in craniotomy patients; maybe because the number of patients in this study was too low.

In summary, the authors of this study implied that DEX infusion before anesthetic induction did not aggravate the decrease in blood pressure, due to propofol infusion. Its hemodynamic effect was obviously no more beneficial than that of fentanyl at 2 µg/kg in craniotomy patients receiving propofol-based anesthesia during endotracheal intubation, skull-pin fixation and skin incision.

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## Conflicts of interest

None

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## ผลของยา dexmedetomidine ต่อการตอบสนองของระบบไหลเวียนโลหิตระหว่างการนำสลบ การใส่หมุดยึดกะโหลกศีรษะและการลงมีดผ่าตัดในผู้ป่วยที่มาผ่าตัดเปิดกะโหลกศีรษะ

อนันท์ชนก ศฤงคารินกุล, ยอดยิ่ง ปัญจะสวัสดิ์วงศ์, ณีภูษิตา คงตันกุล และ กรกมล วีระวงษ์  
ภาควิชาวิสัญญีวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

**วัตถุประสงค์** ผู้วิจัยตั้งสมมุติฐานว่า ยา dexmedetomidine จะช่วยลดการเปลี่ยนแปลงของระบบไหลเวียนโลหิตระหว่างการนำสลบ การใส่หมุดยึดกะโหลกศีรษะ และการลงมีดผ่าตัด ในการผ่าตัดเปิดกะโหลกศีรษะ ส่วนบน เมื่อเปรียบเทียบกับยา fentanyl

**วิธีการศึกษา** ผู้ป่วย 30 ราย อายุ 18-65 ปี นัดหมายมารับการผ่าตัดสมองได้รับยา dexmedetomidine 1 มก./กก. หรือยา fentanyl 2 มก./กก. ทางหลอดเลือดดำก่อนให้ยา propofol ซึ่งเริ่มให้ที่ระดับ 3 มก./กก. โดยเครื่องให้ยาที่ควบคุมระดับยาตามเป้าหมายที่ต้องการและปรับระดับการให้ยา เพื่อรักษาภาวะสลบ โดยใช้เครื่องดัชนีชี้วัดภาวะสลบในผู้ป่วยทั้งสองกลุ่ม ค่าตัวแปรของระบบไหลเวียนโลหิตถูกบันทึกอย่างต่อเนื่องและวิเคราะห์เพื่อหาผลการศึกษา

**ผลการศึกษา** โดยรวมแล้วค่าความดันโลหิต (ซิสโตลิก ไดแอสโตลิกและความดันกลาง) เพิ่มขึ้น หลังจากได้รับยา dexmedetomidine 1 มก./กก. ทางหลอดเลือดดำ ซึ่งมีค่าสูงกว่า ความดันโลหิตในกลุ่มผู้ป่วยที่ได้รับยา fentanyl 2 มก./กก. ตลอดช่วงการศึกษา ซึ่งค่าความดันโลหิตซิสโตลิก ไดแอสโตลิกและความดันกลางของกลุ่ม fentanyl ลดลง หลังจากได้รับยา fentanyl 2 มก./กก. และค่าความดันดังกล่าวลดลงอีกหลังจากนำสลบด้วย propofol แต่ต่อมามีค่าสูงขึ้นตอบสนองต่อการใส่ท่อช่วยหายใจ หลังจากใส่หมุดยึดกะโหลกศีรษะ ค่าความดันไดแอสโตลิกและความดันกลางในผู้ป่วยทั้งสองกลุ่มสูงขึ้น แต่ไม่มีนัยสำคัญทางสถิติเมื่อเทียบกับค่าก่อนใส่หมุดยึดกะโหลกศีรษะในแต่ละกลุ่ม ค่าความดันซิสโตลิก ไดแอสโตลิกและความดันกลางในผู้ป่วยทั้งสองกลุ่ม ไม่เปลี่ยนแปลงไปมากหลังการลงมีดผ่าตัด เทียบกับค่าก่อนการลงมีดผ่าตัด ปริมาณยา propofol ที่ใช้ในการนำสลบและที่ใช้ทั้งหมดในกลุ่มยา dexmedetomidine ไม่น้อยกว่าปริมาณยา propofol ที่ใช้ในกลุ่ม fentanyl ถึงแม้ว่ากลุ่ม dexmedetomidine ต้องการปริมาณยา fentanyl ในระหว่างการผ่าตัดน้อยกว่าเทียบกับกลุ่ม fentanyl แต่ไม่แตกต่างอย่างมีนัยสำคัญทางสถิติ

**สรุปผลการศึกษา** ยา dexmedetomidine ขนาด 1 มก./กก. ไม่ได้มีประสิทธิภาพเหนือกว่ายา fentanyl 2 มก./กก. ในการลดการตอบสนองของระบบไหลเวียนโลหิตต่อการนำสลบด้วยยา propofol การใส่หมุดยึดกะโหลกศีรษะและการลงมีดผ่าตัด **เชียงใหม่เวชสาร 2558;54(1):1-7.**

**คำสำคัญ:** ยา dexmedetomidine การตอบสนองของระบบไหลเวียนโลหิต การใส่หมุดยึดกะโหลกศีรษะ การผ่าตัดเปิดกะโหลกศีรษะ