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Comparison of dexmedetomidine and fentanyl to prevent haemodynamic response to skull pin application in neurosurgery: double blind randomized controlled trial

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Abstract

Background: Skull pin application during craniotomy is a highly noxious stimulus. Therefore, the attenuated effect between dexmedetomidine and fentanyl was investigated.

Methods: A randomized, double-blind controlled trial included sixty patients, randomly allocated into groups A and B. After patients entered the operative room, blood pressure and heart rate were measured (T1). At 5 minutes after propofol induction (T2), group A received dexmedetomidine 1 μg kg^{-1} whereas group B received normal saline. At 3 minutes before skull pin insertion (T3), group B received a single bolus of fentanyl 1 μg kg^{-1} whereas group A received normal saline. The hemodynamic responses were recorded at 1 minute before skull pin insertion (T4), during skull pin insertion (T5), then repeated every minute for 5 minutes (T6-T10).

Results: Controlling blood pressure in the dexmedetomidine group (Group A) was better than in the fentanyl group (Group B) at T4 and T10 ($P < 0.05$) and T5-T8 ($P < 0.01$) for systolic blood pressure whereas diastolic blood pressure was significantly different at T4 and T8 ($P < 0.05$) and T5-T7 ($P < 0.01$). Mean arterial pressure, also was better controlled in group A at T4 and T10 ($P < 0.05$) and T5-T8 ($P < 0.01$). The heart rate in group A was lower than group B at T9 ($P < 0.05$) and T3-T6 ($P < 0.01$). Regarding adverse events, 11 hypertensive and 2 hypotensive responses occurred in group B whereas group A just only had 7 incidences of hypotension.

Conclusion: The attenuated effect of dexmedetomidine infusion is significantly greater than fentanyl infusion.

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Key words: skull pin application, haemodynamic response; alpha-2 receptor, agonists, dexmedetomidine; opioids, fentanyl

The skull pin head holder is applied for the steady positioning of the patient's head during neurosurgical procedures. The application of skull pins takes place through the scalp and the periosteum into the external layer of skull. Although the skull pins are applied after induction of general anaesthesia, this stimulus induces a haemodynamic change including tachycardia and increased blood pressure;. Furthermore, this stimulus can lead to brain oedema, increased intracranial pressure, and intracerebral haemorrhage [1]. Various anaesthetic techniques and pharmacological agents have been proposed to attenuate these deleterious effects. These techniques include infiltration of local anaesthesia of the pin sites [2], scalp block [3], and deepening the level of anaesthesia [4]. Regarding pharmacological agents, there are numerous agents including opioids [5–7], alpha agonist [1, 8], beta-blockers [9], and gabapentin [10] for controlling haemodynamic changes. In particular, opioids and alpha-agonists are widely used. Fentanyl is part of a high-potency opioid group. It has been applied to attenuate the haemodynamic response to skull pin placement [11, 12] whereas dexmedetomidine and α2-adrenergic receptor agonists have been used as sedative agent with analgesic properties, for haemodynamic stability, and the preservation of respiratory function [13]. Hence, we designed this study to compare the attenuated effect between fentanyl and dexmedetomidine to determine

which produced the most stable haemodynamic situation during skull pin application.

METHODS

The study was reviewed and approved by the Khon Kaen University Ethics Committee for Human Research (HE581303). Furthermore, this study was registered at ClinicalTrials.gov (NCT03077503). This was a prospective, randomized, double-blind controlled trial in which 60 patients who were scheduled for elective craniotomy under general anaesthesia were enrolled. Patients of either gender aged between 18 and 64 years, belonging to the American Society of Anesthesiologists' (ASA) physical status classifications of I and II were included. Exclusion criteria included the following: patients having a body mass index of more than 30 kg m^{-2}; heart rate lower than 45 bpm; hypertension; ischemic heart disease; heart block; being on beta-adrenergic blockers; as well as an allergy to medication including propofol, fentanyl, and dexmedetomidine. This study was designed with block of four randomizations. The random numbers were generated by computer and concealed in sealed envelope. After written informed consent was obtained, all patients were allocated into two groups. In the induction period, group A received dexmedetomidine 1 µg kg^{-1} (Precedex, Pfizer, USA) diluted to 20 mL with 0.9% NaCl for 10 minutes through a syringe pump; whereas group B received 20 mL of 0.9% NaCl. Three minutes before the application of skull pins, group A received an infusion of 2 mL of 0.9% NaCl whereas group B received an infusion of fentanyl 1 µg kg^{-1} (Fresofol, Kern Pharma, Spain) diluted to 2 mL with 0.9% NaCl. These study drugs were prepared by an anaesthetist nurse who was not involved in the study.

All of patients had been asked to take nil by mouth for 6 hours prior to surgery. In the operating room, monitoring was established regarding blood pressure, electrocardiogram, pulse oximetry, end-tidal carbon dioxide, and arterial blood pressure. All patients received 100% oxygen for 3 minutes before induction with fentanyl 2 µg kg^{-1}, 2% lidocaine 1.5 mg kg^{-1}, propofol 2 mg kg^{-1}, cisatracurium 0.15 mg kg^{-1}, and the study drug following the details described as above. Subsequently, an endotracheal tube was intubated and connected to anaesthetic circuit with controlled ventilation. The ventilation setting was a respiratory rate of 12 times per minute, a tidal volume of 6–8 mL kg^{-1}, and end-tidal CO_2 of 30–25 mm Hg. Ventilation was assisted with 2% sevoflurane in adjusted oxygen: air flow of 1:1 litre per minute. Before the insertion of skull pins, the study drugs were administration as outlined in the above protocol.

Blood pressure, mean arterial pressure, and heart rate were recorded by a blinded anaesthesiologist at: pre-induction time (T1); 5 minutes after induction (T2); 3 minutes (T3) and 1 minute (T4) before pin insertion; the time during pin insertion (T5); and repeated measurement times every minute for 5 minutes after pin application (T6-T10). Rescue drugs were prepared for adverse events. Tachycardia, a heart rate greater than 120 beats per minute, was treated with esmolol of 3 mg titration while 0.3 mg of atropine was titrated to treat bradycardia (heart rate lower than 45 beats per minute). The titration of 3 mg of ephedrine treated blood pressure lower than 90/60 mm Hg. If blood pressure rose higher than 160/90 mm Hg, a rescue dose of 0.5 mg kg^{-1} of propofol was titrated.

A sample size of 24 subjects in each group was deemed appropriate considering 95% confidence intervals, 2% error, and a significance of mean difference between the two groups of 10.7; however, we added 20% of all subjects to cover those predicted to drop out.

RESULTS

Patient demographics are displayed in Table 1. The patients in both groups seem similar. Haemodynamic data, including blood pressure, mean arterial pressure, and heart rate were compared between the two groups. Systolic blood pressure in the dexmedetomidine group (Group A) was con-

Table 1. Demographic data and ASA physical status

Demographic data	Group A (n = 30)	Group B (n = 30)
Age (mean ± SD)	45.40 ± 9.00 years	45.50 ± 10.49 years
Male/Female (n)	7/23	7/23
BMI (mean ± SD)	24.02 ± 3.50 kg m^{-2}	24.37 ± 3.80 kg m^{-2}
Operation time (mean + SD)	202.6 ± 67.8 minutes	214.5 ± 99.8 minutes
Smoking (n)	1	1
Allergy (n)	1	1
ASA physical status		
I (n)	19	16
II (n)	11	14

Table 2. Adverse hemodynamic effect and rescue drugs

Adverse hemodynamic effect	Group A (n = 30)	Group B (n = 30)	*P*-value
Hypertension	0	11 (36.7 %)	< 0.01
Tachycardia	0	0	1.000
Hypotension	7 (23.3%)	2 (6.7%)	0.073
Bradycardia	0	0	1.000
Rescue drugs			
Propofol	0	11 (36.7%)	< 0.01
Ephredine	7 (23.3)	2 (6.7)	0.073
Atropine	0	0	1.000
Esmolol	0	0	1.000

trolled in a range of 103–130 mm Hg, whereas the fentanyl group (Group B) displayed a controlled blood pressure in a range of 107–140 mm Hg. This resulted in a significant statistical difference at T4 and T10 ($P < 0.05$) and T5-T8 ($P < 0.01$). Regarding controlling diastolic blood pressure, the dexmedetomidine groups (Group A) displayed a controlled diastolic pressure in a range of 63–78 mm Hg; whereas, the fentanyl group (group B) displayed a controlled diastolic pressure in a range 66–87 mm Hg. This different outcome was statistically significant at T4 and T8 ($P < 0.05$) and T5-T7 ($P < 0.01$). The range of mean arterial pressure in the dexmedetomidine group (Group A) was 77–96 mm Hg whereas the fentanyl group (Group B) displayed a controlled mean arterial pressure of 80–105 mm Hg. The different mean arterial pressures between the two groups were statistically significant at T4 and T10 ($P < 0.05$) and T5-T8 ($P < 0.01$). The range of the heart rate at 62–81 bpm in the dexmedetomidine group (Group A) was lower than the fentanyl group (Group B) at 71–82 bpm with a statistically significant difference at T9 ($P < 0.05$) and T3-T6 ($P < 0.01$).

All of the adverse haemodynamic effects are presented in Table 2. Although hypertension only occurred in the fentanyl group (Group B) ($P < 0.01$), the dexmedetomidine group (Group A) had more hypotension events than the fentanyl group (Group B) ($P > 0.05$). For treatment of these adverse effects, propofol was used for controlling hypertension ($P < 0.01$) while ephedrine was administrated to rescue hypotension ($P > 0.05$).

DISCUSSION

Skull pin application during neurosurgical procedures is a highly noxious stimulus. It induces haemodynamic changes and may lead to intracranial complications. Control of haemodynamic response is a great concern for neuroanesthesiologists who aim to achieve optimal cerebral blood flow. Many methods have been proposed for controlling haemodynamic responses. Fentanyl is one of the medicines that has been used to control the haemodynamic response to skull pin application. The attenuated effect of fentanyl was demonstrated by Özköse *et al.* [12]. Forty-five patients were allocated into three groups, namely a fentanyl group (2 μg kg^{-1} infusion), a lidocaine group (1% lidocaine infiltration at the pin sites); and the last group (combination of fentanyl and lidocaine). The result showed that the combination group was the best at controlling haemodynamic response. However, just only fentanyl infusion can control the haemodynamic response. Yildiz *et al.* [11] compared a fentanyl infusion group and the combination of fentanyl infusion and bupivacaine infiltration at the pin sites. They found that the haemodynamic response to skull pin insertion was effectively suppressed with both methods. Regarding dexmedetomidine, it also has a powerful effect for controlling haemodynamic response to skull pin application. El Dawlatly *et al.* [14]. compared the effect of low-dose intravenous dexmedetomidine and/or local lidocaine infiltration on haemodynamic responses to skull pin placement. They reported that although the combination of low-dose dexmedetomidine infusion and local lidocaine infiltration seemed to be the best at controlling the haemodynamic response, there was no statisticallly significant difference in either the dexmedetomidine group or the lidocaine group. Wang *et al.* [15]. conducted a meta-analysis in order to review the effects of dexmedetomidine on outcomes following craniocerebral operations. They found that dexmedetomidine can attenuate the haemodynamic response and preserve brain function. These studies demonstrated that although fentanyl and dexmedetomidine have a great attenuated effect on stabilizing the haemodynamic response to skull pin application, comparing the attenuating effect of both drugs was unclear. Sarincaringkul *et al.* [16]. allocated 15 patients to two groups, including a dexmedetomidine group (1 μg kg^{-1}) and a fentanyl group (2 μg kg^{-1}) before propofol-based anaesthesia was administered. They reported that a statisti-

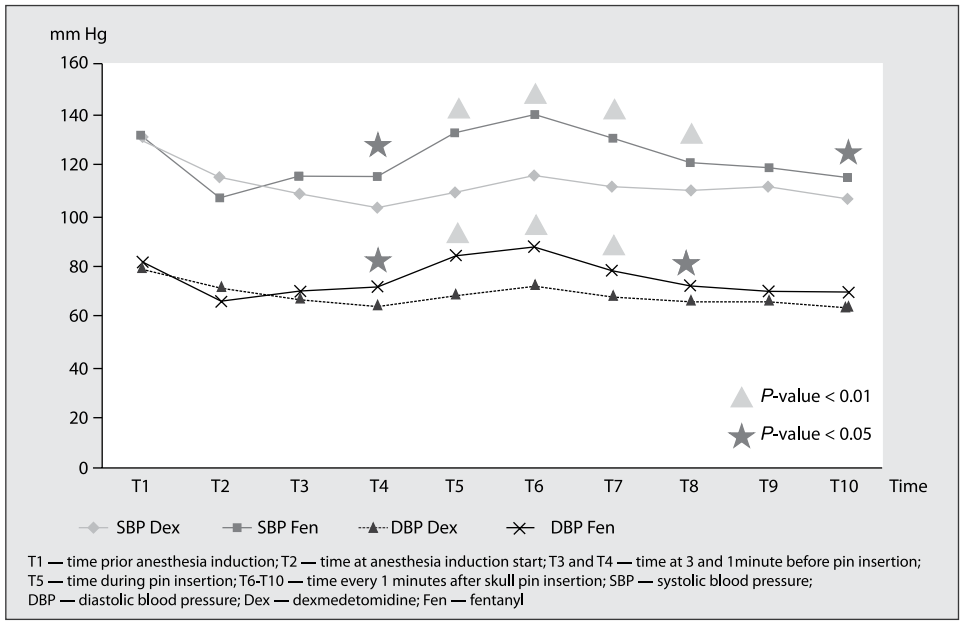

Figure 1. Comparison of the attenuated effect of dexmedetomidine and fentanyl for controlling blood pressure

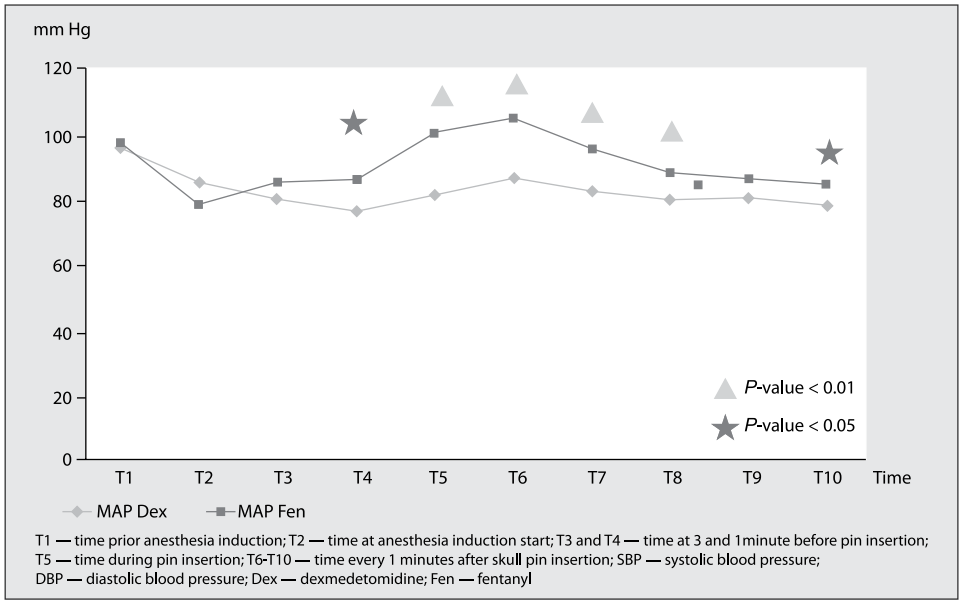

Figure 2. Comparison of the attenuated effect of dexmedetomidine and fentanyl for controlling mean arterial blood pressure

cally significant difference could not be achieved due to the limitation of the sample size being too small. Therefore, we designed a randomized controlled trial with an adequate enrolled sample size to indicate the difference in the attenuated effect of dexmedetomidine and fentanyl. Sixty patients were allocated into two groups. The result showed that the attenuated effect of the dexmedetomidine group was greater than the fentanyl group with a statistically significant difference ($P < 0.05$). The haemodynamic responses during (T5) and after (T6-T10) skull pin application were observed as lower and narrower ranges in the dexmedetomidine group (SBP 107–116 mm Hg; DBP 64–72 mm Hg; MAP 78–87 mm Hg; HR 67–71 bpm) than in the fentanyl group (SBP 115–140 mm Hg; DBP 70–87 mm Hg; MAP 85–105 mm Hg; HR 71–82 bpm). Regarding adverse events, we found that incidences of hypertension only occurred in the fentanyl group (n = 11) whereas hypotension events were greater in the dexmedetomidine group (n = 7) than in the fentanyl group (n = 2) ($P > 0.05$). This result was similar to the study of Paul and Krishna [1] who compared dexmedetomidine infusion and local lidocaine infiltration. They reported that the incidence of

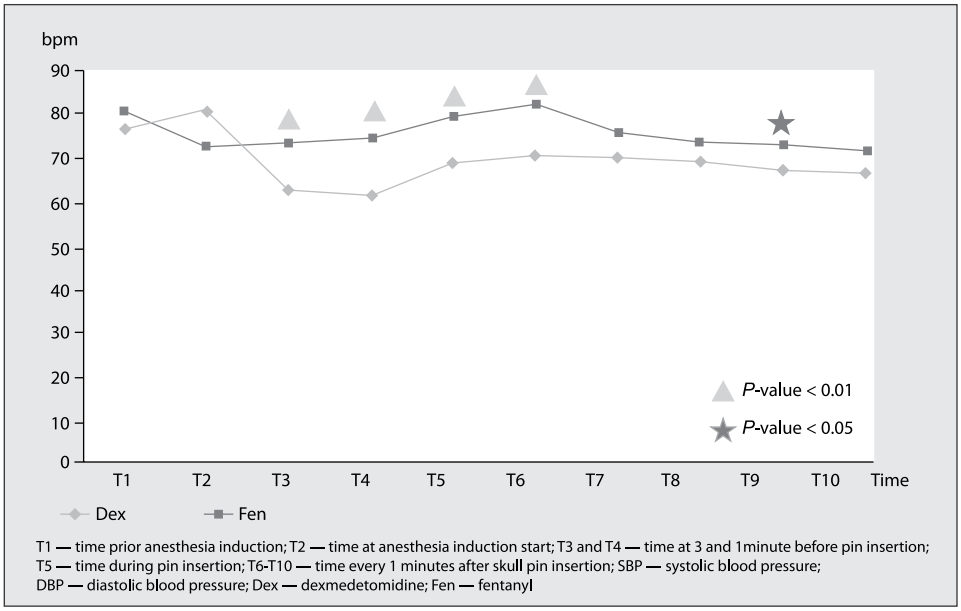

Figure 3. Comparison of the attenuated effect of dexmedetomidine and fentanyl for controlling heart rate

hypotension and/or bradycardia was significantly greater in the dexmedetomidine group (19 patients in the dexmedetomidine group and 5 patients in the lignocaine group; $P = 0.0007$). However, hypotension may not be an adverse effect from dexmedetomidine in all cases as, occasionally, the haemodynamic response to skull pin application can manifest itself as bradycardia or hypotension [1].

CONCLUSION

The attenuated effect of dexmedetomidine infusion (1 μg kg^{-1}) is significantly greater than fentanyl infusion (2 μg kg^{-1}) in order to stabilize haemodynamic response after skull pin application. However, hypotension events have a higher incidence in the dexmedetomidine group. Thus, the administration of dexmedetomidine should be used with caution, especially in patients with cardiovascular disease.

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3. Conflicts of interest: none.
4. Presentation: Preliminary data for this study were presented as an oral presentation at the 32nd Annual Khon Kaen University Faculty of Medicine Academic Conference, October 11-13, 2016, Faculty of Medicine, Khon Kaen University, Thailand.

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