Original Article

Haemodynamic changes and incisional bleeding after scalp infiltration of dexmedetomidine with lidocaine in neurosurgical patients

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ABSTRACT

Background: The purpose of this randomised controlled study is to compare the haemodynamic changes and the degree of incisional bleeding after scalp infiltration of lidocaine and dexmedetomidine versus lidocaine and epinephrine for patients with hemi-facial spasm undergoing microvascular decompression.

Methods: Fifty-two patients were injected with 5 mL of 1% lidocaine with either dexmedetomidine (2 μg/mL) or epinephrine (1:100,000 dilution) to reduce scalp bleeding. Mean blood pressure and heart rate were recorded every minute for 15 minutes after scalp infiltration. The primary outcome was the incidence of predefined hypotension, which was treated with administration of 4 mg ephedrine as often as needed. The number of administrations and total amount of ephedrine administered were also recorded as a measure of the severity of hypotension. The neurosurgeon scored incisional bleeding by numeric rating scale from 0 (worst) to 10 (best).

Results: The incidence of hypotension (68% vs. 34.8%, $P = 0.02$) and the frequency ($P = 0.02$) and total dose ($P = 0.03$) of ephedrine administered were lower in the dexmedetomidine group than in the epinephrine group. In addition, there was no difference in mean blood pressure between the two groups but heart rates were lower in the dexmedetomidine group ($P = 0.01$). Incisional site bleeding was better with epinephrine (median [interquartile range] of the numeric rating Score: 6 [4] in the dexmedetomidine group and 8 [2] in the epinephrine group; $P < 0.001$).

Conclusion: The dexmedetomidine-lidocaine combination may be recommended as a substitute for epinephrine-lidocaine for scalp infiltration in neurosurgical patients, especially neurologically compromised patients.

1. Background

Epinephrine is commonly co-injected with local anaesthetic agent into the scalp to reduce bleeding from scalp incision for craniotomy. However, injection of this mixture can be accompanied by undesirable cardiovascular effects such as transient hypotension caused by vasodilatation in skeletal muscle mediated by β2-adrenoreceptor [1–4]. Epinephrine with lidocaine can lead to profound hypotension in the period after general anaesthesia due to a lack of noxious stimulation.

Local injection of dexmedetomidine, a highly selective α2-adrenoreceptor agonist with sedative, anaesthetic, and analgesic properties [5,6], induces constriction of the peripheral blood vessels mediated by α2A-adrenoreceptor [7]. In a recent animal study, the vasoconstrictive potency of locally injected dexmedetomidine was comparable to that of epinephrine in oral mucosal tissue [8]. However, the peripheral vasoconstrictive and sympatholytic properties of dexmedetomidine may result in various haemodynamic effects, including transient hypertension, bradycardia, and hypotension [9]. Local injection of lidocaine with dexmedetomidine for maxillofacial surgery reduced bleeding from

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the surgical site and controlled the hemodynamic variables better than dexmedetomidine alone, with high surgeon satisfaction [10]. However, there has been no report on the use of dexmedetomidine for scalp injection in neurosurgical patients.

This study investigated the hemodynamic changes and the degree of incisional bleeding after infiltration of lidocaine with either dexmedetomidine or epinephrine into scalp tissue for patients with hemi-facial spasm undergoing microvascular decompression.

2. Methods

After obtaining approval from the Institutional Review Board (ref: 4-2012-0062), the study was registered at ClinicalTrials.gov (ref: NCT01606969). Written informed consent was obtained from all patients.

A total of 52 patients aged 20–70 years and American Society Anaesthesiologist classification I–II who were scheduled for microvascular decompression due to hemi-facial spasm were prospectively enrolled in this study. The exclusion criteria included hypertension with resting blood pressure 140/90 or higher, cardiac conduction disorders above the first atrioventricular block, bradycardia of less than 50 beats per minute, and taking β-blocking agents. Patients were randomly allocated into the dexmedetomidine group (n = 26) or the epinephrine group (n = 26) using an Excel®-generated randomisation table. Two anaesthesiologists participated in intervention and data collection. One anaesthesiologist who knew the group assignment of patients prepared the drug combinations for scalp injection. A second anaesthesiologist who was blinded to the patient group collected the data. The degree of incisional bleeding was scored by the neurosurgeon, who was blinded to the patient group.

Anxiolytic premedication was not used. Upon arrival at the operating room, the patient was monitored with electrocardiography, pulse oximetry, non-invasive blood pressure, and capnography. General anaesthesia was induced with propofol 1.5 mg/kg and remifentanil at an effect site concentration (Ce) of 4 ng/ml using a commercial Target Controlled Infusion system (Fresenius Vial, Brezins, France) incorporating Minto's pharmacokinetic model. After intravenous administration of rocuronium 0.6 mg/kg, the patient was intubated and ventilated mechanically under anaesthetic maintenance with sevoflurane-remifentanil. Mechanical ventilation was adjusted to maintain end-tidal CO_2 of 34–37 mmHg. A forced-air warming system (Augustine-Medical, Eden Prairie, USA) was applied throughout surgery to maintain the body temperature at 36.0–37.0 °C. After skull pinning in surgical positioning and the mean arterial pressure was within 20% of pre-operative baseline values for more than 3 minutes continuously, the experiment was initiated. During the experiment, anaesthesia was maintained at an age-adjusted anaesthetic depth of 0.7 minimal alveolar concentration (MAC) sevoflurane in a 50% oxygen/air mixture and remifentanil Ce of 1.5 ng/mL. If bispectral index (BIS VISTA Monitoring System Inc, Norwood, USA) was outside the target range of 45–55, the sevoflurane concentration was adjusted.

The neurosurgeon drew around a 7.5 cm curved incision line at the retro-mastoid area and injected the experimental solutions subcutaneously. The experimental solutions were 5 mL of 1% lidocaine with either dexmedetomidine (2 μg/mL) or epinephrine (1:100,000 dilution).

In this experiment mean blood pressure and heart rate were recorded every minute for 15 minutes after scalp infiltration. If mean arterial blood pressure decreased by more than 20% of pre-operative baseline values (defined as hypotension), 4 mg of ephedrine was administered repeatedly until resolution. If mean arterial blood pressure increased by more than 20% of pre-operative baseline values (defined as hypertension), 0.2 mg of nicardipine was administered repeatedly until resolution. If bradycardia below 40 beats per minute occurred, 0.5 mg of atropine was administered. The occurrence of haemodynamic changes such as hypotension, hypertension, and bradycardia requiring rescue agent administration was recorded. The primary outcome in this study was the incidence of hypotension during the assessment period. The number of administrations and total amount of ephedrine administered during the experimental period were recorded. To assess the severity of hypotension, the frequency and total dose of ephedrine administered to hypotensive patients were analysed. At the time of craniectomy, the neurosurgeon scored the incisional bleeding using a numeric rating scale ranging from 0 (worst) to 10 (best).

Preliminary data from 18 patients revealed that the incidence of hypotension after administration of epinephrine and dexmedetomidine was 67% and 22%, respectively. Based on these values, the sample size was estimated to be 52 subjects, with 80% power at the 5% significance level and considering 15% loss of study participants. Statistical analyses were performed using the SAS software package, version 9.2 (SAS Institute Inc., Cary, USA). The repeated haemodynamic data between two groups were analysed using a generalised linear mixed model and the scores of incisional bleeding were analysed using a Mann-Whitney U-test. A P-value < 0.05 was considered statistically significant.

3. Results

Of the 52 patients enrolled in this study, four were excluded due to severe hypotension during anaesthetic induction or intra-operative event. Therefore, 48 patients successfully completed the study, (Fig. 1) and their characteristics can be found in Table 1.

The incidence of hypotension (8/23 patients, 34.8% vs. 17/25 patents, 68%, P = 0.02) as well as frequency (P = 0.02) and total dose (P = 0.03) of ephedrine administered were lower in the dexmedetomidine group than the epinephrine group (Table 2). However, regarding the severity of hypotension, there was no difference in the number of administrations and total amount of ephedrine administered among the hypotensive patients of the two groups (P = 0.63 and 0.98, respectively).

The changes in mean arterial blood pressure after scalp injection were not different between the two groups (P = 0.13) (Fig. 2). However, mean blood pressure of both groups decreased gradually after scalp injection compared to the pre-infiltration value. The changes in heart rate were significantly greater in the epinephrine group than in the dexmedetomidine group at all time points after scalp injection (P = 0.01). None of the patients required nicardipine or atropine administration because of hypertension or bradycardia.

The median [interquartile range] of Numeric Rating Score for incisional site bleeding was 8 [2] in the epinephrine group and 6 [4] in the dexmedetomidine group (P < 0.001) (Fig. 3).

4. Discussion

We compared haemodynamic changes and the degree of incisional bleeding after scalp infiltration of a mixture of lidocaine with either dexmedetomidine or epinephrine in patients with hemi-facial spasm undergoing retro-mastoid craniectomy. The dexmedetomidine group showed a lower incidence of hypotension than the epinephrine group. However, the vasoconstrictive condition of the incisional site was better in the epinephrine group than in the dexmedetomidine group.
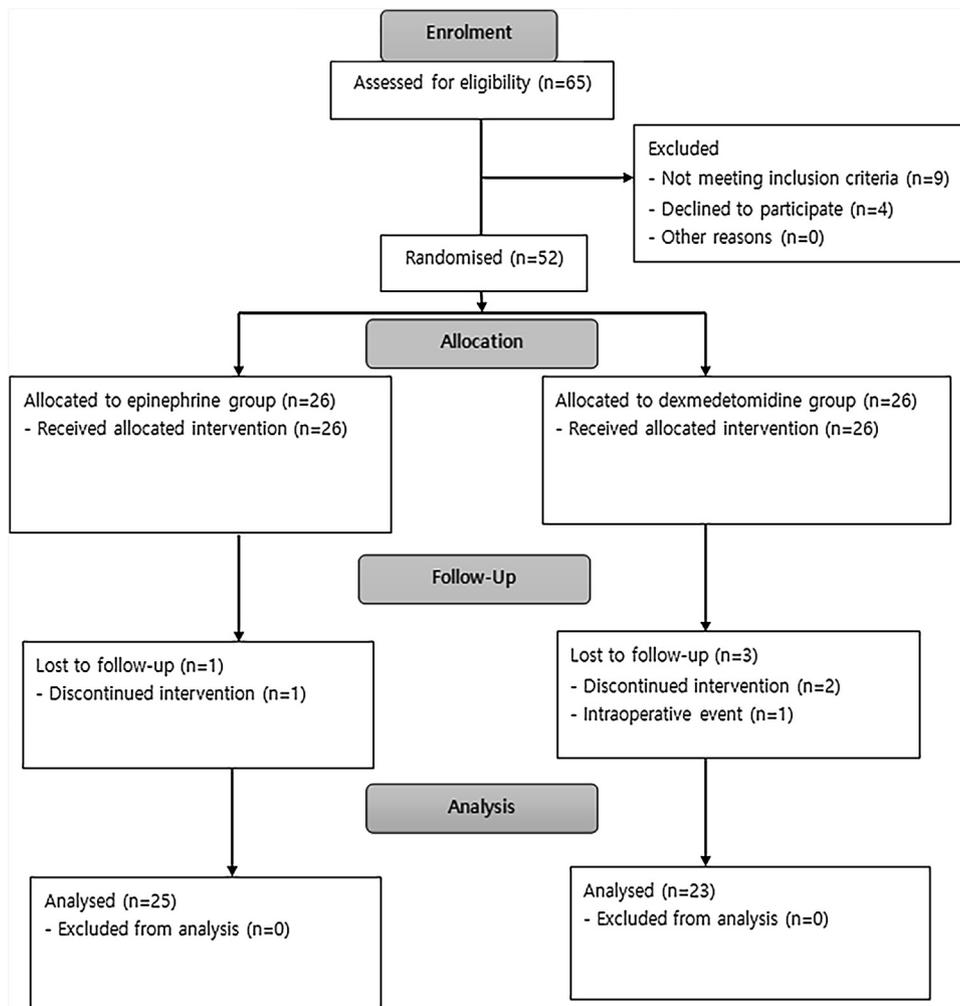
Fig. 1. Consolidated Standard of Reporting Trials flow diagram of the study.

For craniotomy, scalp infiltration of lidocaine with or without vasoconstrictors is commonly performed to reduce incisional bleeding and blunt the haemodynamic responses to incisional stimuli. However, hypotensive episodes can occur when epinephrine is used, probably due to the action of lidocaine to potentiate β_2 effect of epinephrine [4,11]. The occurrence of hypotension itself is detrimental to neurologically compromised patients. In addition, it is still unclear whether the systemic use of dexmedetomidine is protective or harmful in these patients [12–14]. We wondered whether scalp infiltration of lidocaine with dexmedetomidine would show different haemodynamic changes from lidocaine with epinephrine. As an ancillary issue, dexmedetomidine may also decrease incisional bleeding comparable to the effect of epinephrine due to its vasoconstrictive property. Therefore, we performed this study to determine whether a dexmedetomidine-lidocaine mixture could be a substitute for epinephrine-lidocaine for scalp infiltration in neurosurgical patients, especially compromised patients.

In previous studies, the addition of dexmedemetomidine to a local anaesthetic affected the distribution of blood flow in peripheral tissue and thereby influenced pharmacokinetic and pharmacodynamics variables of the anaesthetic [8,15,16]. Akimoto et al. [8] performed an elaborate study in rats to examine the influence of dexmedetomidine on pharmacologic and anaesthetic actions of lidocaine using radioactive ^{14}C-labelled lidocaine. Following infiltration of 2% lidocaine with either dexmedetomidine (at three concentrations of 3.1, 12.5, and 50 μg/mL) or epinephrine (at 1:100,000 dilution) into the palatal mucosa, dexmedetomidine in lidocaine solution induced vasoconstriction and thereby allowed retention of lidocaine for longer in peripheral

Table 1
Demographic data of participants.

|	Epinephrine ($n = 25$)	Dexmedetomidine ($n = 23$)	P-value
Age (years)	53 (10)	53 (7)	0.98
Sex (male/female)	7/18	4/19	0.39
Height (cm)	159 (6)	159 (7)	0.81
Weight (kg)	61 (9)	60 (10)	0.61
ASA classification (?/?)	17 / 8	13 / 10	0.42
Pre-operative mean arterial pressure (mmHg)	89 (9.3)	91 (9.8)	0.41
Pre-induction heart rate (bpm)	69 (8.6)	70 (8.2)	0.77

Table 2
Comparison of hypotension incidence and ephedrine requirements.

	Epinephrine (n = 25)	Dexmedetomidine (n = 23)	P-value
Incidence of hypotension (%)	68.0%	34.8%	0.02[a]
Number of ephedrine administration in median (IQR)	1 (1)	0 (1)	0.02[a]
Total amount of ephedrine (mg) in median (IQR)	4 (4)	0 (4)	0.03[a]

Values are proportion or median (IQR).
IQR: interquartile range.
[a] $P \leq 0.05$
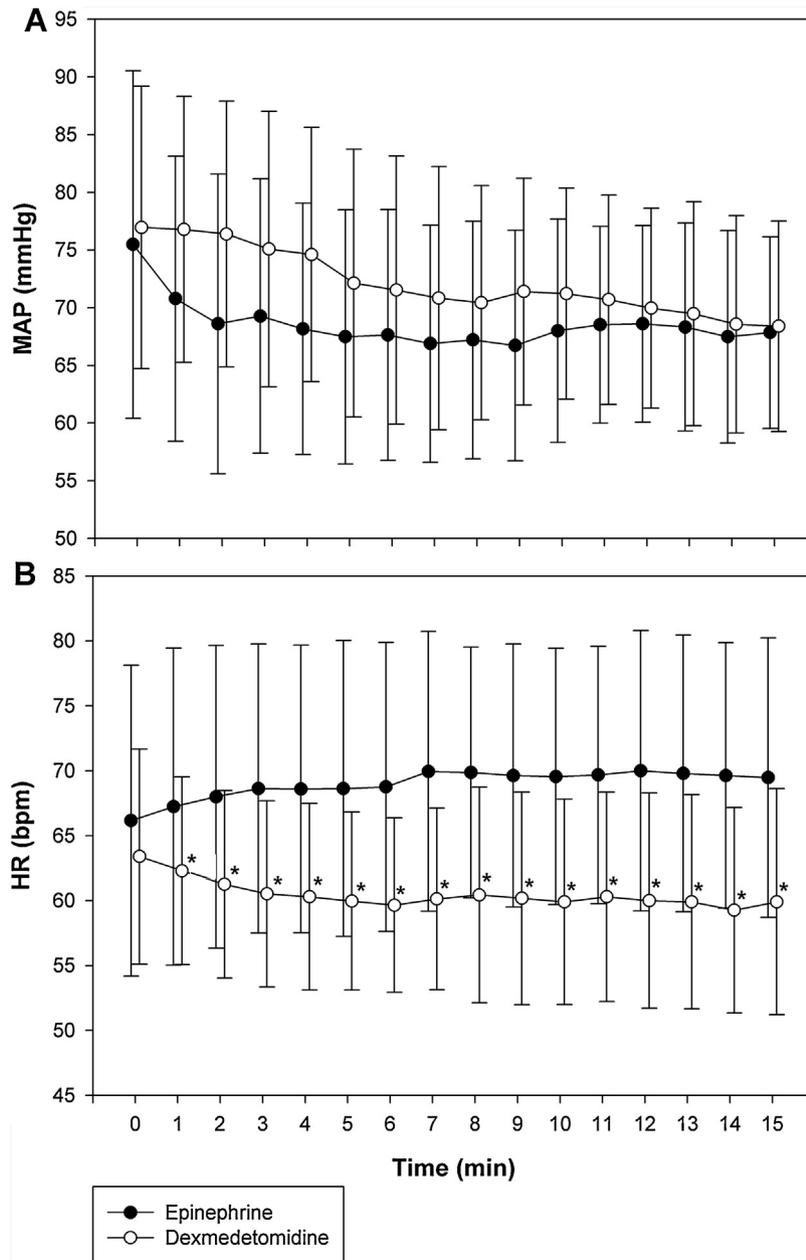
Fig. 2. Changes in mean blood pressure (A) and heart rate (B) after scalp injection in the epinephrine group (●) and the dexmedetomidine group (○). MAP, mean arterial pressure, bpm, beats per minute, Time 0, at moment of scalp infiltration. Bar represents standard deviation. *$P < 0.05$.

tissue. The 12.5 μg/mL concentration of dexmedetomidine presented a similar vasoconstrictive effect to 10 μg/ml epinephrine, and was suggested as an appropriate substitution for 1:100,000 epinephrine in dental lidocaine infiltration anaesthesia. In clinical situations, dexmedetomidine reduced surgical bleeding and improved surgical field condition through local infiltration [10]

or systemic infusion. [17] To the authors' knowledge, the present study is the first clinical trial to compare the hemodynamic changes and vasoconstrictive properties of dexmedetomidine with those of epinephrine as an additional agent for scalp infiltration of lidocaine. The incidence of hypotension was lower in the dexmedetomidine group than the epinephrine group together
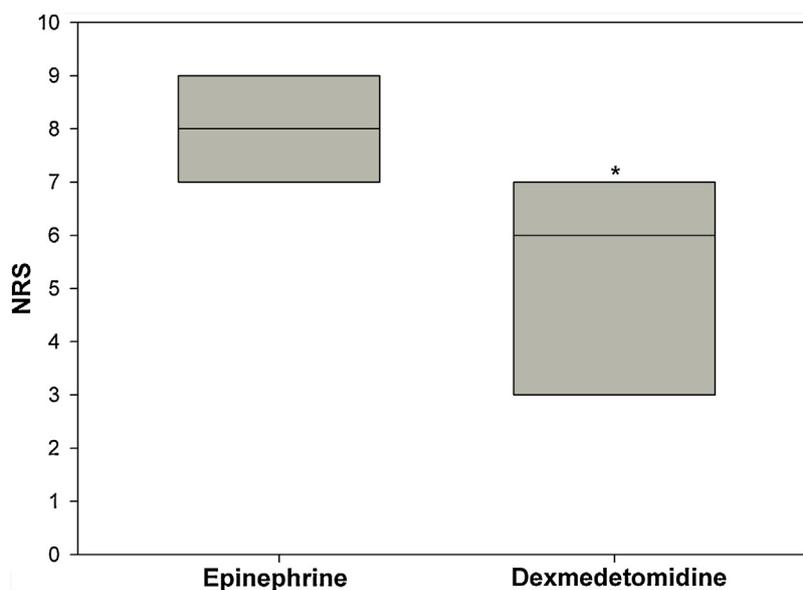
Fig. 3. Numeric rating score for incisional bleeding as median (interquartile range). NRS: numeric rating score, NRS 0, worst, NRS 10, best. $^{*}P < 0.001$.

with a lower frequency and total dose of rescue ephedrine. However, there was no difference in the frequency and dose of ephedrine administered in hypotensive patients of both groups. The mean blood pressure was lower in the epinephrine group but without significance, and decreased gradually in both groups. However, we could not confirm whether the insignificantly lower mean blood pressure in the epinephrine group contributed to the better incisional bleeding score. Furthermore, we do not know the clinical significance of the difference of bleeding score between epinephrine and dexmedetomidine groups.

In contrast to previous studies, [1–3] the haemodynamic changes of the epinephrine group in this study were relatively stable, possibly due to the small dose of epinephrine and lidocaine used.

The hemodynamic effects of systemic administration of dexmedetomidine showed a dose-dependent biphasic pattern of a short increase in mean blood pressure followed by long-lasting hypotension. The reduced norepinephrine release resulted in a decrease in vascular tone and hypotension with a low dose of dexmedetomidine, whereas at a high dose of dexmedetomidine it produced α-2B adrenoceptor mediated vasoconstriction and hypertension. However, the mechanism of vasoconstriction and stable blood pressure after local infiltration of lidocaine with dexmedetomidine seems to be rather complex, and activation of α-2A receptor may result in central hypotension whereas both the α-2A and α-2B adrenoceptor in the vasculature mediate peripheral vasoconstriction [18–20].

In conclusion, our study suggests that an epinephrine-lidocaine mixture may be substituted by dexmedetomidine-lidocaine for scalp infiltration in neurosurgical patients, especially hemodynamically compromised patients or especially in patients with a low blood pressure.

Ethical Statement for Solid State Ionics – Diffusion and Reactions

This material has not been published in whole or in part elsewhere; the manuscript is not currently being considered for publication in another journal; all authors have been personally and acticely involved in substantive work leading to the manuscript, and will hold themselves jointly and individually responsible for its content.

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