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NEUROSCIENCES AND NEUROANAESTHESIA

Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery: a double-blind, randomized and placebo-controlled study†

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Background. Dexmedetomidine (DEX) has been shown to provide good perioperative haemodynamic stability with decreased intraoperative opioid requirements. It may have neural protective effects, and thus may be a suitable anaesthetic adjuvant to neurosurgical anaesthesia.

Methods. Fifty-four patients scheduled for elective surgery of supratentorial brain tumour were randomized to receive in a double-blind manner a continuous DEX infusion (plasma target concentration 0.2 or 0.4 ng ml^{-1}) or placebo, beginning 20 min before anaesthesia and continuing until the start of skin closure. The DEX groups received fentanyl 2 μg kg^{-1} at the induction of anaesthesia and before the start of operation, the placebo group 4 μg kg^{-1}, respectively. Anaesthesia was maintained with nitrous oxide in oxygen and isoflurane.

Results. The median times from the termination of N_2O to extubation were 6 (3–27), 3 (0–20) and 4 (0–13) min in placebo, DEX-0.2 and DEX-0.4 groups, respectively ($P<0.05$ ANOVA all-over effect). The median percentage of time points when systolic blood pressure was within more or less than 20% of the intraoperative mean was 72, 77 and 85, respectively ($P<0.01$), DEX-0.4 group differed significantly from the other groups. DEX blunted the tachycardic response to intubation ($P<0.01$) and the hypertensive response to extubation ($P<0.01$). DEX-0.4 group differed in the heart rate variability from placebo (93 *vs* 82%, $P<0.01$).

Conclusions. DEX increased perioperative haemodynamic stability in patients undergoing brain tumour surgery. Compared with fentanyl, the trachea was intubated faster without respiratory depression.

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The goals of neuroanaesthesia are to provide good operating conditions and to ensure stable cerebral haemodynamics without sudden increases in intracranial pressure or acute brain swelling. Furthermore, fast recovery from anaesthesia is often preferred to allow immediate neurological evaluation. During recovery, abrupt increases in arterial blood pressure can pose a risk for postoperative haematoma.[1] Opioid analgesia prevents haemodynamic responses to awakening and extubation but may result in respiratory depression and high carbon dioxide tension with subsequent increase in the intracranial pressure.[2]

α_2-Adrenergic agonists have been introduced to clinical anaesthesia for their sympatholytic, sedative, anaesthetic sparing and haemodynamic stabilizing properties.[3] Dexmedetomidine (DEX) has shown analgesic effects without significant respiratory depression.[4 5] As DEX provides good perioperative haemodynamic stability with decreased intraoperative opioid requirements,[6 7] and studies in animals suggest that it may have other beneficial effects in terms of

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neural protection,[8 9] it might be a suitable anaesthetic adjuvant to neurosurgical anaesthesia.

We hypothesized that craniotomy patients receiving DEX perioperatively would have better preserved respiratory drive and lower Pa_{CO_2} values after operation. We also tested perioperative haemodynamic variability and intraoperative anaesthetic requirements.

Table 1 Assessment of consciousness according to Hudes[13]

1	Awake, nervous patient shows no effect of premedication
2	Awake, not obviously drowsy but the patient claims to feel calmer/drowsy
3	Awake, obviously drowsy to observer
4	Asleep, rouses to verbal stimuli
5	Asleep, rouses to tactile stimuli, and is articulate and coherent
6	Asleep, rouses to tactile stimuli, not able to speak clearly
7	Asleep, not rousing to tactile stimuli

Patients and methods

In this double-blinded, randomized and parallel-group trial, we compared two infusion rates of DEX with placebo. The study was approved by the institutional Ethics' Committee and the Finnish national agency of medicines. A written informed consent was obtained before enrolling the patient in the study.

Any patient aged 20–65 yr, with Glasgow Coma Scale score 14 or 15 and scheduled for elective intracranial surgery of a supratentorial tumour under general anaesthesia in our institution, was considered eligible for the study. The exclusion criteria were as follows: pregnant or nursing woman, or premenopausal woman without reliable contraception; morbid obesity; preoperative heart rate (HR) <45 beats min^{-1}; second or third degree AV block; antihypertensive medication with α-methyldopa, clonidine or other α_2-adrenergic agonist; participation in another drug study during the preceding 1 month period.

Each patient received a continuous i.v. infusion of DEX (two dose levels) or placebo. The DEX infusion rates were designed to achieve and maintain a steady-state plasma DEX concentration of either 0.20 ng ml^{-1} (DEX-0.2 group) or 0.40 ng ml^{-1} (DEX-0.4 group) using Stanpump simulations and Dyck kinetics.[10–12] The infusion was commenced 20 min before the induction of anaesthesia and continued until the start of skin closure.

Balanced randomization using permuted blocks was applied. The study drug and placebo (sodium chloride solution 0.9%) were supplied by the drug manufacturer (Orion-Pharma, Espoo, Finland). In order to keep the investigators blind to the study treatment, the Hospital Pharmacy diluted DEX or placebo with sodium chloride solution 0.9% into a ready-to-use form. In addition, two syringes (one to be given 3 min before induction and the other 3 min before the Sugita frame application or skin incision) each containing 2 μg kg^{-1} fentanyl diluted into a volume of 10 ml were prepared for those patients who received DEX. Similarly, two syringes each containing 4 μg kg^{-1} fentanyl diluted into a volume of 10 ml were prepared for those patients who received the placebo infusion.

Perioperative management

Baseline values for HR, systolic and diastolic blood pressure (SBP and DBP) were recorded at least 8 h before the induction of anaesthesia. Routine medications were continued as clinically indicated. Two hours before transferring the patient to the operating room, all puncture sites were treated with topical local anaesthetic cream (EMLA®, Astra, Sweden). Approximately 1 h before transfer to the operating room, 0.2 mg kg^{-1} (rounded up to the closest 5 mg) of diazepam per *os* was administered. The state of consciousness was assessed on a scale from 1 to 7 (Table 1)[13] immediately before premedication, and subjective sedation was assessed on a visual analogue scale (VAS) from 0 (not tired at all) to 100 (very tired, almost impossible to stay awake). Upon arrival in the operating room, a large bore i.v. catheter was inserted for drug and continuous fluid administration (Ringer's acetate). A radial or femoral artery was cannulated for arterial pressure monitoring and obtaining blood samples. After the assessment of the state of consciousness and subjective sedation, and recordings of SBP, DBP, HR, Sp_{O_2} and obtaining samples for blood gas analysis, the study drug infusion was commenced approximately 20 min before the induction of anaesthesia. During the infusion, SBP, DBP, HR and Sp_{O_2} were recorded at 5 min intervals.

Before the induction of anaesthesia, the state of consciousness and subjective sedation were assessed, and samples for blood gas analysis were obtained. At the induction of anaesthesia the patients received glycopyrrolate (Gastrodyn® 0.2 mg ml^{-1}, Leiras, Finland) 3 μg kg^{-1} i.v. The patients randomized to the DEX groups received fentanyl 2 μg kg^{-1} i.v., and those randomized to the placebo group received fentanyl 4 μg kg^{-1} i.v. in a double-blind manner. Three minutes after administration of fentanyl, anaesthesia was induced with thiopental (Hypnostan® 25 mg ml^{-1}, Leiras, Finland) injected at the rate of 10 ml min^{-1} until the loss of eye lash reflex. The dose of thiopental was recorded. Neuromuscular block was achieved by administering pancuronium 0.1 mg kg^{-1} i.v. (Pavulon® 2 mg ml^{-1}, Organon, Holland). After administration of pancuronium, the patient's lungs were ventilated by mask for at least 3 min using 100% oxygen. Thirty seconds before laryngoscopy and intubation, the patients were given 50 mg of thiopental. Laryngoscopy and intubation were performed when neuromuscular block was sufficient as indicated by train-of-four monitor. During the induction period SBP, DBP, HR and Sp_{O_2} were recorded at 1 min intervals (and also 30 s after laryngoscopy) until 10 min after intubation and at 5 min intervals thereafter. Samples for blood gas analysis were obtained immediately after intubation. End-tidal CO_2 concentration (Capnomac Ultima, Datex, Finland) was recorded immediately after intubation and at 5 min intervals thereafter.

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After intubation 1 g kg^{-1} of mannitol was administered i.v. over approximately 30 min and vancomycin (Vancocin®, Lilly, USA) 1 g i.v. over a 60–120 min period. A urinary catheter was inserted for monitoring of urinary output. Neuromuscular block was maintained with 1–2 mg boluses of pancuronium.

Anaesthesia was maintained with nitrous oxide in oxygen (60%:40%), isoflurane (gradually increased to 0.5% end-tidal concentration) and 0.5 μg kg^{-1} increments of fentanyl. A semi-open ventilation system was used (Servo, Siemens-Elema, Sweden) and the patients' lungs were hyperventilated with the target arterial CO_2 tension of 3.5–4.0 kPa. End-tidal isoflurane concentration was measured continuously (Capnomac, Datex, Finland) and recorded at 5 min intervals, and at 2 min intervals if changed. Hypertension (SBP>140 mm Hg), tachycardia (HR>100 beats min^{-1}) and clinical signs of light anaesthesia (bucking, lacrimation, sweating, flushing and movement) were treated by fentanyl 2.0 μg kg^{-1}. If that was not sufficient within 4 min, the initial isoflurane 0.5% end-tidal concentration was increased by 0.2% every 4 min up to a maximum of 1.1% end-tidal concentration, after which the isoflurane end-tidal concentration was decreased in 0.2% steps every 4 min as long as the values remained in the predetermined limits. If an isoflurane end-tidal concentration of 1.1% was not sufficient to decrease arterial pressure and HR to acceptable values, fentanyl was given in 0.5 μg kg^{-1} increments every 4 min until the predetermined limits were achieved. If hypertension did not respond to treatment with fentanyl, thiopental was administered as clinically indicated. If excessive brain swelling occurred, isoflurane or nitrous oxide or both were discontinued and swelling was treated with additional thiopental as clinically indicated. If hypotension (SBP<90 mm Hg) occurred, ephedrine 5 mg (Efedrin inject® 50 mg ml^{-1}, Kabi Pharmacia, Stockholm, Sweden) was given i.v. Bradycardia (HR<40 beats min^{-1}) was treated with 0.5 mg boluses of atropine (Leiras, Turku, Finland) i.v. titrated to effect.

Surgery of the supratentorial tumour was performed using established techniques. In case of the Sugita frame application, the patients in the DEX groups received fentanyl 2 μg kg^{-1} i.v., and those randomized to the placebo group received fentanyl 4 μg kg^{-1} i.v. in a double-blind manner. Skin was then infiltrated with prilocaine with epinephrine (Citanest 5 mg ml+adrenalin 4 μg ml^{-1} injekt®, AstraZeneca, Södertälje, Sweden). Similarly, if the head frame was not applied, fentanyl was administrated 3 min before skin incision as described above. During these periods, SBP, DBP, HR and Sp_{O_2} were recorded at 1 min intervals until 10 min after head frame application or skin incision and at 5 min intervals thereafter.

Arterial samples for blood gas analyses were obtained at 60 min intervals during surgery.

The exact times of anaesthetic induction, the dose of thiopental and the time of intubation were recorded. The number of interventions occurring when haemodynamic variables were outside the predetermined window were recorded.

Termination of anaesthesia

Isoflurane administration and the study drug infusion were discontinued at approximately 10 min before the estimated end of surgery. At the end of surgery, neuromuscular block was antagonized with metastigmine (Metastigmin® inject 0.5 mg ml^{-1}, Star, Finland) 2 mg i.v. and glycopyrrolate (Gastrodyn® 0.2 mg ml^{-1}, Leiras, Turku, Finland) 0.4 mg i.v. Nitrous oxide administration was discontinued after skin closure when the train-of-four response was 90%. The patient's trachea was extubated when respiration was deemed sufficient and patients were able to obey simple commands. Naloxone (Narcanti® inject 0.4 mg ml^{-1}, DuPont, USA) or doxapram (Dopram® inject 20 mg ml^{-1}, Wyeth, Taplow, UK) were to be administered if clinically considered necessary.

Postoperative treatment

After operation, the patient was transferred to and monitored at the Neurosurgical Intensive Care Unit (NICU). Monitoring included continuous invasive BP monitoring, ECG and pulse oximetry, and the values were recorded at 15 min intervals for the first 2 h and thereafter at 30 min intervals until 6 h in the NICU. Arterial blood samples for blood gas analyses were obtained every 15 min during the first 2 h in the NICU. The neurological status (Glasgow Coma Scale, pupillary size and reactivity, movement and strength of extremities) was evaluated upon arrival at the NICU and at 30–60 min intervals thereafter. Two hours after extubation the state of consciousness (Hudes class) and subjective sedation were assessed.

Assuming sufficient patient sedation and analgesia and adequate fluid balance, haemodynamic abnormalities were treated as presented in Table 2.

Postoperative pain was treated with 2 mg increments of oxycodone (Oxanest®, Leiras, Turku, Finland) i.v. All drugs and fluids administered and all clinical events during the first six postoperative hours were recorded.

A 10 ml venous blood sample was obtained for determination of serum DEX concentration before and 20, 60, 120 and 240 min after the start of the study drug infusion, and

Table 2 Postoperative interventions upon haemodynamic changes

Haemodynamic abnormality		Intervention
Bradycardia	Heart rate <40 beats min^{-1}	Atropine 0.5 mg increments
Hypotension	SBP <90 mm Hg	Ephedrine 5 mg increments
Tachycardia	Heart rate >100 beats min^{-1}	Labetalol 10 mg increments
Hypertension	SBP >180 mm Hg	Dihydralazine 6.25 mg increments
Hypertension and tachycardia		Labetalol 10 mg increments

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Table 3 Patient characteristic variables. Mean (SD) of means or the numbers of patients are presented. No significant differences between the groups

	Placebo group	DEX-0.2 group	DEX-0.4 group
Sex (male/female)	11/7	7/10	8/10
Age (yr)	43 (12)	47 (11)	47 (9)
Weight (kg)	74 (11)	71 (11)	72 (8)
Height (cm)	172 (8)	170 (9)	171 (9)

Table 4 Mean (SD) serum concentrations of dexmedetomidine in a subset of patients

Time (min)	DEX-0.2 group (ng ml^{-1})	*N*	DEX-0.4 group (ng ml^{-1})	*N*
20	0.28 (0.06)	8	0.58 (0.09)	8
60	0.27 (0.03)	8	0.54 (0.01)	9
120	0.23 (0.05)	8	0.41 (0.01)	9
240	0.20 (0.05)	2	0.38 (0.05)	4

after that at 1 h intervals until 3 h after operation in a subset of patients in DEX groups. The DEX concentrations were analysed using gas chromatography–mass spectrometry. The lower limits of detection were 50 pg ml^{-1} and the intra-assay coefficients of variation were 3.3%.

Statistical analysis

The sample size was based on the investigators' previous experience in a similar patient population in which mean (SD) postoperative CO_2 was 5.23 (0.52) kPa. According to statistical power analysis, 17 patients per treatment group were needed to get a 80% power in detecting a 10% difference between treatment groups with a 5% type I error. Assuming a 5% dropout rate, the final sample size was set at 54 patients (18 patients per group).

Patient characteristic data were analysed using ANOVA or Fisher's exact test. Generalized Wilcoxon test was used to compare differences between survival curves of event times.

Repeated measures ANOVA was used for analysis of continuous variables. In case of a significant overall treatment effect, post-ANOVA contrasts or pairwise non-parametric tests were used for paired comparisons. Kruskall–Wallis test, one-way ANOVA and Fisher's exact test were used when appropriate. Statistical analyses were performed using SAS 6.12 statistical software for Windows.

A *P*-value <0.05 was considered statistically significant.

Results

One patient was excluded from the study because of protocol violation. Therefore, the records of 53 patients were used for the analysis (Table 3). A Sugita frame was used in 5, 13 and 3 patients in the placebo, DEX-0.2 and DEX-0.4 groups, respectively.

The serum DEX levels were higher than targeted at 20 and 60 min after commencement of the infusion and in the targeted level at 2 and 4 h (Table 4).

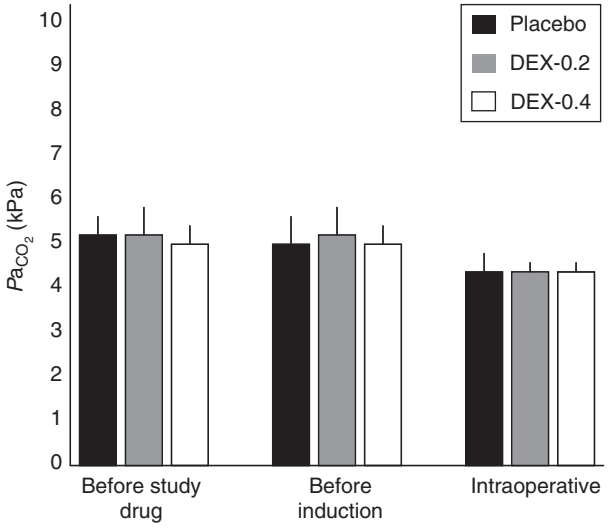

Fig 1 Mean (SD) Pa_{CO_2} during the preoperative and intraoperative period. The differences between the groups and time points were statistically non-significant.

Table 5 The changes in postoperative Pa_{CO_2}. Mean (SD) of means are presented. No differences between the groups or time points

	Placebo group (kPa)	DEX-0.2 group (kPa)	DEX-0.4 group (kPa)
Baseline	5.01 (0.39)	4.99 (0.60)	4.72 (0.41)
15 min	5.57 (0.64)	5.21 (0.76)	5.08 (0.72)
30 min	5.51 (0.65)	5.26 (0.69)	5.08 (0.82)
45 min	5.54 (0.60)	5.19 (0.71)	5.10 (0.80)
60 min	5.57 (0.62)	5.12 (0.92)	5.04 (0.83)
75 min	5.52 (0.54)	5.15 (0.85)	4.94 (0.78)
90 min	5.38 (0.56)	5.24 (0.74)	5.02 (0.80)
105 min	5.47 (0.52)	5.16 (0.67)	4.97 (0.73)
120 min	5.49 (0.54)	5.27 (0.67)	4.98 (0.70)

The median times (range in parentheses) from the induction of anaesthesia to the removal of the tracheal tube were 208 min (131–285 min), 201 min (97–376 min) and 248 min (150–423 min) in the placebo, DEX-0.2 and DEX-0.4 groups, respectively [not significant (NS)]. In the DEX groups the patients' tracheas were extubated faster than those of the placebo group: the median times from the termination of N_2O to extubation were 6 (3–27), 3 (0–20) and 4 (0–13) min in the placebo, DEX-0.2 and DEX-0.4 groups, respectively ($P<0.05$).

There was no difference between the groups in arterial CO_2 tension during the study drug infusion before the induction of anaesthesia (Fig. 1). Pa_{CO_2} increased in all three groups after operation, but there were no significant differences between the groups (Table 5). Naloxone was needed in two patients for respiratory depression in the placebo group. During the 2 h follow-up, the Pa_{O_2} levels remained stable at approximately 20 kPa in all groups, extra oxygen (35%) was routinely provided via mask.

There were no differences between the groups in the increase in systolic blood pressure observed after laryngoscopy and intubation, but the increase in HR was attenuated

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Table 6 Maximum increases from the baseline in systolic blood pressure and heart rate after laryngoscopy and intubation and after extubation. Mean (SD) are presented. $^{**}P<0.01$, DEX-0.4 group *vs* DEX-0.2 and placebo groups; $^{\#\#}P<0.01$, DEX-0.2 and DEX-0.4 groups *vs* placebo group

	Placebo group	DEX-0.2 group	DEX-0.4 group
Systolic blood pressure (mm Hg)			
After laryngoscopy and intubation	28 (24)	39 (28)	31 (24)
After extubation	41 (19)	30 (18)	17 (19)**
Heart rate (beats min^{-1})			
After laryngoscopy and intubation	22 (15)	10 (16)##	5 (15)##
After extubation	15 (20)	12 (19)	6 (19)

Table 7 Intraoperative cardiovascular variability. The median percentage of time points when arterial pressure and heart rate were within more or less than 20% of the preinduction and intraoperative values. Medians (and ranges in parentheses) are presented. $^{*}P<0.01$, DEX-0.4 group *vs* DEX-0.2 and placebo groups; $^{**}P<0.01$ DEX-0.4 group *vs* placebo group

	Placebo group (n=18)	DEX-0.2 group (n=17)	DEX-0.4 group (n=18)
Compared with preinduction values			
SBP (mm Hg)	44 (13–80)	53 (33–84)	71 (31–88)*
DBP (mm Hg)	58 (16–76)	57 (33–85)	73 (17–94)
HR (beats min^{-1})	58 (20–94)	74 (12–99)	83 (40–100)**
Compared with intraoperative values			
SBP (mm Hg)	72 (51–90)	77 (46–90)	85 (66–94)*
DBP (mm Hg)	72 (41–84)	70 (41–85)	81 (62–92)*
HR (beats min^{-1})	82 (66–99)	91 (66–99)	93 (75–100)**

by DEX (Table 6). After extubation, the mean increase in systolic blood pressure was the smallest in the DEX-0.4 group. There were no significant differences between the groups in the HR at extubation (Table 6).

The median percentages of time points when systolic blood pressure, diastolic blood pressure and HR were within more or less than 20% of the preinduction and intraoperative values are presented in Table 7. The DEX-0.4 group was significantly different from DEX-0.2 and placebo groups ($P<0.01$). There was a significant difference in the HR variability only between the placebo and DEX-0.4 groups ($P<0.01$). During the postoperative period, there were no differences between the groups in cardiovascular variability.

The mean induction doses of thiopental were 315 (60), 293 (72) and 297 (63) mg in the placebo, DEX-0.2 and DEX-0.4 groups (NS). Three patients in both DEX groups received an additional 50 mg dose of thiopental at the end of surgery because of bucking against the intubation tube during the removal of Sugita frame. The mean concentrations of end-tidal isoflurane were 0.51 (0.09)% in the placebo group, 0.50 (0.09)% in the DEX-0.2 group and 0.49 (0.03)% in the DEX-0.4 group (NS). The mean amount of additional fentanyl were 2.3 (3.3), 1.7 (2.6) and 1.1 (2.3) $\mu g\ kg^{-1}$, respectively (NS). There were no differences in intraoperative interventions between the groups (Table 8). One patient needed labetalol and one needed atropine during the postoperative period in the placebo group. Labetalol was given

Table 8 Intraoperative interventions. Medians and range or the number of cases are presented. There were no statistically significant differences between the groups

	Placebo group	DEX-0.2 group	DEX-0.4 group
Changes in isoflurane concentration (N)	0 (0–7)	0 (0–6)	0 (0–2)
Ephedrine requirements			
Number of patients	12	11	11
Total dose (mg)	10 (0–25)	5 (0–40)	5 (0–25)
Atropine requirements			
Number of patients	1	1	1
Total dose (mg)	0.5	0.5	0.5
Total number of interventions/patient	4 (0–22)	2 (0–12)	2 (0–6)

in one patient for increased HR, hydralazine in two patients for hypertension and ephedrine in one patient for hypotension in the DEX-0.2 group. One patient received atropine for decreased HR in the DEX-0.4 group. There were no differences in the number of postoperative pharmacological interventions between the groups.

The mean doses of oxycodone for postoperative analgesia were 5.6 (3.5), 6.0 (3.2) and 6.4 (2.8) mg in the placebo, DEX-0.2 and DEX-0.4 groups, respectively (NS).

The VAS scores for subjective sedation increased from baseline by 16 (22), 30 (25) and 40 (30) in the placebo, DEX-0.2 and DEX-0.4 groups, respectively, before the induction of anaesthesia ($P<0.05$). The state of consciousness decreased in both DEX groups as compared with placebo ($P<0.01$): in the placebo group all the patients remained in the Hudes[13] category 1–3, but in the DEX groups there were patients also in categories 4–7. There was no difference between the DEX groups. All the patients were immediately able to obey commands upon arrival into the ICU, except for one patient in the placebo group who needed repeated doses of naloxone to recover (also she was evaluable within 30 min). At 2 h after extubation, there was no difference in the Hudes class or subjective sedation score between the groups.

Discussion

We investigated the effects of DEX in neurosurgical patients in an attempt to find a clinically feasible combination of anaesthetics that would ensure perioperative haemodynamic stability and fast recovery without respiratory depression. Such combination would reduce the required volatile anaesthetic requirements and decrease the risk of affecting cerebral autoregulation. In the present study, we demonstrated that intraoperative DEX infusion decreased haemodynamic responses to various noxious stimuli and attenuated the emergence from anaesthesia both by decreasing the immediate haemodynamic response and the time to removal of the tracheal tube.

DEX is a highly selective α_2-agonist that has been shown to have sedative, analgesic and anaesthetic sparing effects.[5 6 14–17] It causes a dose-dependent decrease in

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arterial blood pressure and HR associated with a decrease in serum norepinephrine concentrations.[18] The effect of α_2-agonists on haemodynamics is biphasic: an immediate increase in systemic arterial pressure (mediated by stimulation of peripheral α_{2B}-adrenoceptors) followed by a longer lasting reduction in pressure caused by stimulation of α_2-adrenoceptors in the central nervous system.[19] These actions may have contributed to the findings in the haemodynamic profile in our patients who received DEX.

The concept of neuroanaesthesia includes several principles, the haemodynamic stability perioperatively being one of utmost importance. During surgery, abrupt increases in arterial blood pressure may cause bleeding or oedema in the operating field. Low arterial pressures on the other hand predispose the patients to cerebral ischaemia, because autoregulation of the cerebral blood flow (CBF) is often impaired near tumours or traumatized areas.[20]

In some earlier reports, oral clonidine (the archetypal alpha$_2$-agent) premedication provided attenuation of the hypertensive response to laryngoscopy and intubation and head holder application in patients undergoing supratentorial surgery.[21 22] In patients undergoing general or gynaecological surgery, numerous studies have shown that DEX blunts the cardiovascular responses to intubation,[6 15 23] and our findings in craniotomy patients were in accordance with them. In addition to this theoretically beneficial property of alpha$_2$-agonists, they have also been reported to increase the risk of hypotension and bradycardia. These effects have most often been seen in young healthy volunteers or after rapid bolus administration.[4 19 23] In our study there was no difference between the groups in the occurrence of bradycardia or hypotension.

The haemodynamic responses to intracranial surgery are most often elicited at the beginning or the end of the procedure. Similarly, the manipulation of certain structures within the brain may produce cardiovascular changes. During supratentorial tumour surgery such responses are infrequent, however. In the present study, the need to treat hypertension or tachycardia was similar in all groups. DEX has been widely studied as an anaesthetic adjuvant, and its anaesthetic sparing effects are well known. In numerous studies, it has been shown to reduce the isoflurane requirements dose-dependently up to 90%.[15–17] It has also been shown that DEX potentiates analgesia caused by fentanyl in animals[7 24] and reduces its dose requirements in humans during surgery.[6] The fentanyl dose in the placebo group was twice that given in the DEX groups, as it was considered unethical not to provide adequate analgesia to the placebo group. Although it was not our main interest to study the well-demonstrated anaesthetic sparing effect, it became apparent also in our results, as the haemodynamic stability was better maintained in the DEX groups receiving less fentanyl, compared with the placebo group.

After surgery, hypertension may predispose the patient to postoperative intracranial haematomas.[1] The haemodynamic responses to emergence from anaesthesia and extubation are blunted with DEX,[23 25] and the centrally mediated sympatholytic effect has continued well into the postoperative period.[23] Also, in our study, DEX attenuated cardiovascular responses to the emergence from anaesthesia, but the advantageous effect did not extend to the recovery period.

'The golden standard' of neuroanaesthesia includes maintenance of anaesthesia with isoflurane or propofol with fentanyl.[26] Recently, new alternatives, such as sevoflurane, desflurane and remifentanil, have been introduced to this paradigm. High concentrations of volatile anaesthetics can blunt the carbon dioxide response and render CBF pressure passively.[27] Even with low concentrations, hyperventilation is needed to counteract the vasodilation caused by the volatile anaesthetics, to avoid increases in the intracranial pressure in patients with mass occupying lesions. In dogs, administration of DEX significantly attenuated isoflurane- and sevoflurane-induced dilation of cerebral arterioles.[28] In the present study, we administered isoflurane in concentrations less than 1 MAC, and also moderate hyperventilation was used.

In the present study, we used fentanyl for intraoperative analgesia because it has little effect on CBF regulation. When used in high doses, however, it may cause delayed awakening and respiratory depression. Remifentanil, on the other hand, is rapidly metabolized and is compatible with quick awakening,[29] but the abrupt termination of remifentanil analgesia may cause hypertension at emergence from anaesthesia and during the immediate postoperative period.[30] When the dose of fentanyl was reduced and DEX was used in an attempt to control the haemodynamics, the immediate recovery was faster.

DEX has been shown to have minimal effects on respiration,[4 5] and ventilatory weaning and tracheal extubation has been succesfully carried out in critically ill patients under continuing DEX sedation.[31] We started the DEX infusion 20 min before the induction of anaesthesia, and a marked sedative effect was seen without any significant increases in arterial carbon dioxide partial pressure. Thus, DEX does not bear a risk of increasing intracranial pressure by hypoventilation in patients with mass occupying lesions. In healthy volunteers breathing 5% CO_2 mixture, an increase in the minute ventilation was observed during DEX infusion.[32] Furthermore, the inhibition of the hypercapnic cerebral vasodilation by DEX may be beneficial in neurosurgical patients.[33] In our study, the patients in the DEX groups had their tracheal tubes removed more quickly than patients in the placebo group. The difference of a few minutes, although statistically significant, is probably not clinically important. It may, however, reflect the lack of respiratory depression of DEX.[32] Indeed, no patient in the DEX groups needed naloxone, but two patients in the placebo group did. There was no difference between the groups in the arterial carbon dioxide tensions after operation, again indicating its diminutive effects on the respiratory drive.

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Limitations of the study

Estimating the anaesthetic depth by changes mediated by autonomic nervous system (e.g. increases in arterial pressure and HR) is difficult during DEX anaesthesia as it increases haemodynamic stability. In our series there were no cases of awareness, suggesting adequate anaesthetic depth. BIS monitoring was not used, as during craniotomy intracranial air may interfere with the method. The isoflurane concentrations were similar, and the number of changes in concentration did not differ between the groups in our study (Table 8). As DEX has been shown to reduce the MAC of inhalation anaesthestics[34] and the need of perioperative fentanyl,[6] we believe that the difference in the amount of fentanyl may have been compensated for with DEX. However, the requirement for thiopental at the end of the surgery and the trend towards higher postoperative oxycodone doses in the DEX groups may indicate that the intraoperative combinations of fentanyl and DEX were not equianalgesic across the three groups. Also, at all time points there was a clear trend towards lower postoperative Pa_{CO_2} values in the DEX groups than in placebo group, with lower values in DEX-0.4 than DEX-0.2 (Table 5). Although the differences were not statistically significant, unequal analgesia or better preserved respiratory function may have occurred.[32] Unfortunately, the postoperative pain-scores were not recorded. However, as the total dose of oxycodone was only about 6 mg in all the groups, there probably would not have been clinically significant difference in the pain scores across the groups. Retrospectively, the hypothesis of the study may have been overenthusiastic. As adequate spontaneous respiration was prerequisite for tracheal extubation, our assumption that DEX-treated patients would have had even lower (though only by 10%) postoperative Pa_{CO_2} values was unsubstantiated.

Despite greater haemodynamic stability in the DEX groups, there still were numerous occasions of intraoperative hypertension and tachycardia needing treatment in all groups. Perhaps these responses could have been prevented by a higher dose of DEX, as it has been reported to potentiate the depressive effect of halothane on the hypertensive response to stimulation of pressor sites in the central nervous system in experimental animals.[35] We compared two concentrations of DEX used with low-dose fentanyl to a 'high-dose' fentanyl group (placebo). We chose DEX target concentrations 0.2 and 0.4 ng ml^{-1} based on a previous study,[36] where comparable concentrations offered increased perioperative haemodynamic stability in high-risk vascular surgery patients. Doses up to 0.6–0.7 ng ml^{-1} target concentration have been used without serious untoward effects.[15–17] The upper limit seems to be around 1.0–1.2 ng ml^{-1} plasma concentration, at which the persistent peripheral vasoconstriction and hypertension become apparent.[4 15 37]

Controversy exists about the neuroprotective effects of DEX. In animal studies, DEX has improved neurological outcome from transient incomplete and focal ischaemia.[8 9] This effect has been related to reduced sympathetic outflow, and it has been shown that a reduction in circulating catecholamines rather than cerebral catecholamine concentrations mediate neuroprotection after cerebral ischaemia.[38] On the other hand, DEX is a direct cerebral vasoconstrictor that may override the cerebral pressure autoregulation.[39] In a recent study using positron emission tomography DEX decreased global CBF in human volunteers while at the same time decreasing systemic arterial pressure and cardiac output.[40] This may predispose to cerebral ischaemia, although in animal studies the vasodilatory response to hypoxia has been preserved.[33] DEX has been successfully used for sedation during awake craniotomy,[41] but in patients undergoing awake carotid endarterectomy, the need for shunting was 3-fold in the DEX-sedated patients (NS because of the small number of patients).[42]

This study protocol does not allow us to make any conclusions about possible neuroprotective or cerebral vasoconstrictive effects of DEX in elective supratentorial tumour patients. We have, however, demonstrated the safety and feasibility of DEX in these patients in terms of cardiorespiratory stability. Larger outcome studies on neural protection are warranted in clinical settings.

In conclusion, DEX significantly attenuated the haemodynamic responses to intubation and the emergence from anaesthesia. In addition, it increased intraoperative cardiovascular stability. Most of the effects were concentration-dependent, and the higher dose was more effective than the lower dose. Patients receiving DEX had their tracheal tubes removed faster than those in the placebo group, indicating preserved respiratory function.

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