ORIGINAL ARTICLE

A multicentre, randomised, open-label, controlled trial evaluating equivalence of inhalational and intravenous anaesthesia during elective craniotomy

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Context A clear preference for intravenous or inhalational anaesthesia has not been established for craniotomy in patients without signs of cerebral hypertension.

Objectives The NeuroMorfeo trial was designed to test equivalence of inhalational and intravenous anaesthesia maintenance techniques in the postoperative recovery of patients undergoing elective supratentorial surgery.

Design This trial is a multicentre, randomised, open-label, equivalence design. A balanced stratified randomisation scheme was maintained using a centralised randomisation service. Equivalence was tested using the two one-sided tests procedure.

Setting Fourteen Italian neuroanaesthesia centres participated in the study from December 2007 to March 2009.

Patients Adults, 18 to 75 years old, scheduled for elective supratentorial intracranial surgery under general anaesthesia were eligible for enrolment if they had a normal preoperative level of consciousness and no clinical signs of intracranial hypertension.

Interventions Patients were randomised to one of three anaesthesia maintenance protocols to determine if sevoflurane–remifentanil or sevoflurane–fentanyl were equivalent to propofol–remifentanil.

Main outcome measures The primary outcome was the time to achieve an Aldrete postanaesthesia score of at least 9 after tracheal extubation. Secondary endpoints included haemodynamic parameters, quality of the surgical field, perioperative neuroendocrine stress responses and routine postoperative assessments.

Results Four hundred and eleven patients [51% men, mean age 54.8 (SD 13.3) years] were enrolled. Primary outcome data were available for 380. Median (interquartiles) times to reach an Aldrete score of at least 9 were 3.48 (2.02 to 7.56), 3.25 (1.21 to 6.45) and 3.32 min (1.40 to 8.33) for sevoflurane–fentanyl, sevoflurane–remifentanil and propofol–remifentanil anaesthesia respectively, which confirmed equivalence using the two one-sided tests approach. Between-treatment differences in haemodynamic variables were small and not clinically relevant. Urinary catecholamine and cortisol responses had significantly lower activation with propofol–remifentanil. Postoperative pain and analgesic requirements were significantly higher in the remifentanil groups.

Conclusion Equivalence was shown for inhalational and intravenous maintenance anaesthesia in times to reach an Aldrete score of at least 9 after tracheal extubation. Haemodynamic variables, the quality of surgical field and postoperative assessments were also similar. Perioperative endocrine stress responses were significantly blunted with propofol–remifentanil and higher analgesic requirements were recorded in the remifentanil groups. Trial registration: Eudract 2007–005279-32.

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Introduction

Anaesthesia for neurosurgical procedures needs to provide adequate cerebral oxygenation and a stable haemodynamic state. Rapid emergence from anaesthesia is also desirable to permit early postoperative evaluation. Rapid recovery is promoted by inhalational anaesthesia, whereas intravenous (i.v.) anaesthesia promotes brain relaxation and results in less interference with electrophysiological monitoring.[1] Currently, propofol–opioid and sevoflurane–opioid combinations are the most frequently used combinations for neurosurgical procedures.[2] Limited data are available from randomised clinical trials to support a clear superiority for either treatment.[3–5] Talke *et al.*[6] reported similar recovery and psychomotor performances in 60 patients undergoing

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The study results have been partially presented at the Simposio Mostra Anestesia, Rianimazione e Terapia Intensiva meeting (http://www.smartonweb.org), Milano, May 2010. The trial design has been published on Trials (Citerio G, Franzosi MG, Latini R, Masson S, Barlera S, Guzzetti S, Pesenti A. Anaesthesiological strategies in elective craniotomy: randomised, equivalence, open trial – the NeuroMorfeo trial. Trials 2009; 10:19).

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elective surgery for supratentorial mass lesions randomised to propofol infusion, isoflurane inhalation or combined therapy. Most patients achieved an Aldrete score of at least 9 within 15 min of completion of anaesthesia. Magni *et al.*[4] likewise reported similar times to emergence and early cognitive ability in 120 patients randomised to sevoflurane–fentanyl or propofol–remifentanil for supratentorial craniotomy. Recently, Lauta *et al.*[5] used the Aldrete postoperative score as the primary outcome in 302 patients undergoing neurosurgery for supratentorial neoplasms assigned randomly to anaesthesia with sevoflurane–remifentanil or propofol–remifentanil. Median times to reach an Aldrete score of at least 9 were similar at 5 min with both anaesthetic techniques. Other studies have failed to demonstrate superiority for inhaled or i.v. anaesthesia using additional outcome measures.[7]

To date, no trial has directly tested equivalence of inhalational and i.v. anaesthesia. An equivalence trial tests whether treatments or interventions differ by predefined margins. The NeuroMorfeo trial was therefore designed to test equivalence of inhalational and i.v. anaesthesia in patients without cerebral hypertension undergoing elective supratentorial surgery. The primary outcome was defined as time to achieve an Aldrete score of at least 9 after tracheal extubation. Secondary outcomes included haemodynamic responses, endocrine stress responses, the quality of the surgical field, incidences of perioperative adverse events and patient satisfaction scores.

Materials and methods

The NeuroMorfeo trial was a multicentre, randomised, open-label study with an equivalence design registered with Eudract (2007-005279-32, 12.10.2007) and AIFA registries (FARM6FKJKK), with G.C. as principal investigator. The study was conducted from December 2007 to March 2009. Fourteen Italian neuroanaesthesia centres participated in the study. The study was approved by local ethical review boards and the trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation for Good Clinical Practice. Written informed consent was obtained from each patient prior to enrolment. Full study methods have been published previously[8] and will be summarised below.

Ethics

The Ethical Committee of A.O. San Gerardo, Monza, Italy (Chairperson Dr V. Crespi), approved this study on 13 September 2007 (Protocol v.1.2 – 27 August 2007).

Patients

Adults, 18 to 75 years old, scheduled for elective supratentorial intracranial surgery under general anaesthesia were eligible for enrolment if they had a normal preoperative level of consciousness, defined as Glasgow Coma Scale score of 15, and no clinical signs of intracranial hypertension. Exclusion criteria included severe cardiovascular, renal or liver disease, pregnancy, allergies to any anaesthetic agent, body weight more than 120 kg, drug abuse or psychiatric conditions and documented disturbance, or surgery of the hypothalamic region. Patients were also excluded if their condition warranted planned awakening in the ICU, postoperative sedation or postoperative mechanical ventilation. All potential candidates were enrolled at least 1 day prior to surgery.

Interventions

Patients were randomised 1 : 1 : 1 to one of three anaesthesia protocols: sevoflurane with fentanyl (S–F), sevoflurane with remifentanil (S–R) or propofol with remifentanil (P–R). Balanced randomisation was maintained at each clinical site using a stratified randomisation scheme provided by a centralised randomisation service. Patients were randomised on the day before scheduled surgery.

Before induction, all patients were premedicated with i.v. midazolam 5 mg. Anaesthesia was induced with i.v. propofol 2 to 3 $mg\,kg^{-1}$ and cisatracurium 0.1 to 0.2 $mg\,kg^{-1}$, with additional fentanyl 2 to 4 $\mu g\,kg^{-1}$ for patients randomised to S–F and remifentanil 0.25 $\mu g\,kg^{-1}min^{-1}$ infused for 3 min before induction for patients randomised to S–R or P–R. In all patients, the lungs were ventilated mechanically using a closed breathing system (fresh gas flow of 0.75 $l\,min^{-1}$ oxygen and 1.5 $l\,min^{-1}$ air) to achieve an end-tidal carbon dioxide of tension 4.0 to 4.6 kPa. No local anaesthesia was permitted.

Anaesthesia was maintained as follows:

(1) S–F: sevoflurane 0.75 to 1.25 minimal alveolar concentration (MAC) and fentanyl 2 to 3 $\mu g\,kg^{-1}\,h^{-1}$ −1 or 0.7 $\mu g\,kg^{-1}$ boluses
(2) S–R: sevoflurane 0.75 to 1.25 MAC and remifentanil 0.05 to 0.25 $\mu g\,kg^{-1}\,min^{-1}$ reduced to 0.05 to 0.1 $\mu g\,kg^{-1}\,min^{-1}$ after dural opening
(3) P–R: propofol infused continuously at 10 $mg\,kg^{-1}\,h^{-1}$ for 10 min, reduced to 8 $mg\,kg^{-1}\,h^{-1}$ for 10 min, and then reduced to 6 $mg\,kg^{-1}\,h^{-1}$ for the remainder of the procedure and remifentanil infused at 0.05 to 0.25 $\mu g\,kg^{-1}\,min^{-1}$, reduced to 0.05 to 0.1 $\mu g\,kg^{-1}\,min^{-1}$ after dural opening

Supplemental treatments with fentanyl for S–F or remifentanil for S–R or P–R groups were permitted immediately prior to incision of the scalp. Neuromuscular blockade was obtained during surgery with cisatracurium, which was discontinued once the bone flap was secured. The protocol involved maintaining the mean arterial pressure (MAP) between 65 and 85 mmHg and the doses of the anaesthetics and analgesics was varied accordingly. At the end of surgery, residual neuromuscular blockade was antagonised with neostigmine 2.5 mg and atropine

1 mg. Sevoflurane and propofol infusions were reduced once the bone flap was secured and stopped at skin dressing. Fentanyl was stopped at skin dressing and remifentanil reduced at skin dressing by 30% every 3 to 4 min. An i.v. infusion of paracetamol 1 g was started in all patients before bone flap repositioning. In the remifentanil groups, i.v. morphine 0.03 to 0.1 mg kg^{-1} was also given. Postoperative analgesia was permitted using morphine or fentanyl in the recovery room and stepwise administration of paracetamol, ketoprofen or morphine during the first 24 h after surgery. The study groups and doses reflect the clinical practice of the participating centres and had been defined during preparatory meetings of all the investigators.

Biomarkers

Circulating biomarkers of stress were measured in urine and plasma samples collected before induction of anaesthesia, during surgical procedures and immediately after awakening of the patients, according to the protocol. The concentrations of the urinary markers were normalised to urine creatinine concentration measured using an automated colorimetric Jaffé method. All the assays were performed in a single batch in a central laboratory with personnel blind to patients and treatment allocation.

Study endpoints

The primary endpoint was the time to reach an Aldrete score of at least 9 after tracheal extubation. The Aldrete score quantifies recovery after anaesthesia using several domains (mobility, respiration, oxygenation, cardiovascular stability and consciousness), with a postoperative score of at least 9 generally accepted as adequate.[6,9–12] The Aldrete scoring system is widely accepted and has been used as an outcome measure in previously published randomised controlled trials comparing outcomes after i.v. or inhaled anaesthesia during craniotomy.[3,5] To minimise bias in assessing treatment effects, a prospective randomised open blinded endpoint (PROBE) design was used in which primary endpoint data were assessed by anaesthesiologists not involved in the case and blinded to treatment assignment.[13]

Secondary endpoints included haemodynamic stability, endocrine stress biomarkers, brain relaxation, adverse events, patient satisfaction and costs. Circulating stress biomarkers (cortisol and catecholamine concentrations) were measured in urine and plasma samples collected before induction of anaesthesia, during surgical procedures, and immediately after the patients awoke. Brain relaxation was assessed at dural opening by a neurosurgeon blinded to study group, using a 4-point brain relaxation score adapted from a previously published comparative trial: 1 = relaxed brain; 2 = mild brain swelling, acceptable; 3 = moderate brain swelling, no therapy required; 4 = severe swelling, requiring treatment.[3] Intraoperative adverse events were classified as: arterial hypotension (MAP <50 mmHg) or hypertension (MAP >95 mmHg), bradycardia (<50 beats min^{-1}) or tachycardia (>95 beats min^{-1}) and uses of osmotic therapies or hyperventilation (end-tidal carbon dioxide tension <4.0 kPa) to reduce brain swelling. Immediate postoperative assessment of adverse events included recording the occurrences of seizures, cough, shivering, agitation and postoperative pain. Pain was rated using a 10-point numeric rating scale, with scores of at least 7 signifying severe pain. Adverse events recorded during the first 24 h after surgery included the immediate postoperative adverse events, and delirium and postoperative haematoma. Patient satisfaction was assessed 24 h after surgery using the Iowa Satisfaction with Anaesthesia Scale.[14,15] Drug costs were estimated for each treatment by determining typical total drug costs (based on national Italian government service standards) for an uncomplicated procedure in a patient weighing 70 kg requiring anaesthesia for 5 h.

Statistical methods

The trial was designed to test whether S–R or S–F were equivalent to P–R for the time required to reach an Aldrete score of at least 9 after tracheal extubation. The sample size was determined for the primary outcome of time after tracheal extubation to achieve an Aldrete score of at least 9, with plausible lower and upper equivalence limits for the mean difference of −3 to +3 min and a pooled SD of 7 min for both comparisons using previously published data.[3,8] A sample size of 411 patients (137 in each group) was calculated to provide power of at least 84% to conclude equivalence, assuming a 10% dropout rate and an overall type I error (α) of 0.05, setting the α level at 0.025 for each of the two comparisons. An intent-to-treat (ITT) analysis with an additional per-protocol analysis for patients treated without major protocol deviations was conducted. As the two approaches gave similar results, the ITT analysis was considered definitive and only ITT results are reported.

Patient demographics were evaluated using descriptive statistics. Baseline characteristics in groups were compared using χ^2 or Fisher exact test for categorical variables and by analysis of variance (ANOVA) or nonparametric Kruskal–Wallis test for continuous variables. Between-treatment outcomes were compared for inhalational and i.v. anaesthesia (S–F vs. P–R and S–R vs. P–R). Data on the times to reach an Aldrete score of at least 9 were expressed as median and interquartile range (Q1–Q3). As the distribution of the Aldrete score showed a right skewness, as has been similarly observed in previously published results,[16] the data were transformed to natural logarithms. A centre effect was tested using two-way ANOVA with the centre as a cofactor. To evaluate whether the mean differences in the times to

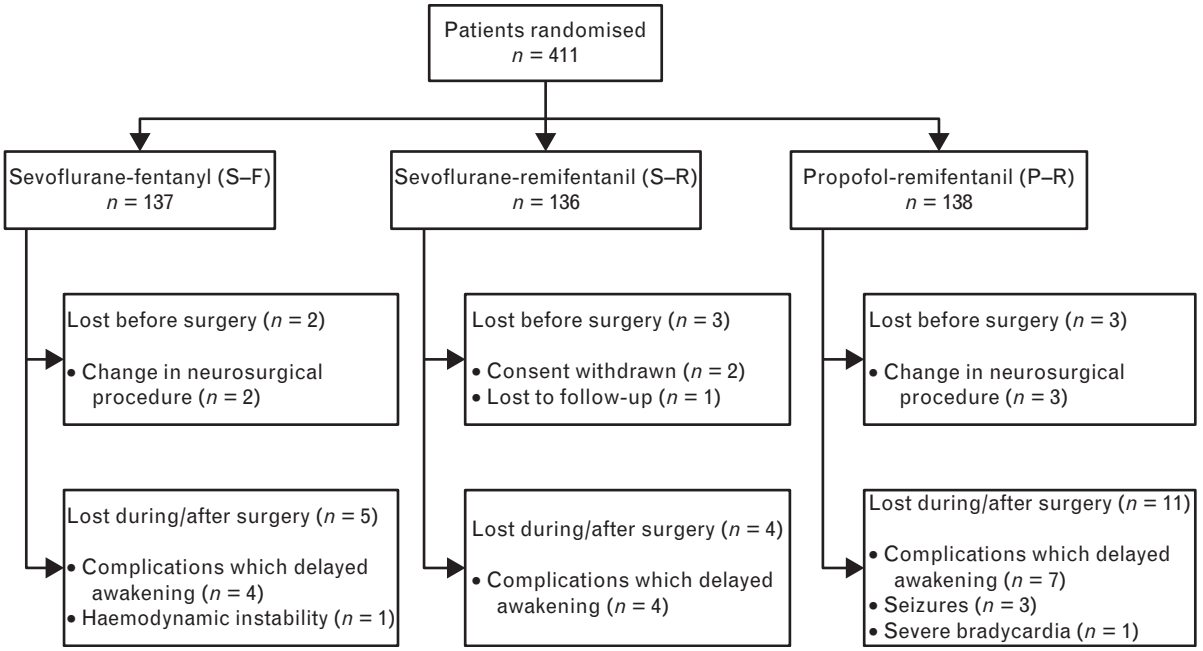
reach the Aldrete score of at least 9 were equivalent between study groups, Student's *t*-tests were performed, applying the two one-sided tests (TOST) procedure for log-normal distribution at an α level of 0.025, as homogeneity of variances among the three randomised groups was satisfied.[17] *P* values for equivalence testing were calculated for each comparison using Schuirmann's TOST for log-normal data. Mean differences with 95% confidence intervals (CIs) were calculated on a logarithmic scale and then back-transformed to the original scale.

Repeated measures ANOVA general linear models were used to analyse changes over time in heart rate and SBP, which enabled main effects to be evaluated (i.e. time, anaesthesia, interaction time × anaesthesia) and are reported with adjusted Greenhouse–Geisser *P* values. Data were analysed at fixed time points including baseline, tracheal intubation, dura mater opening, duration of surgery (mean time), dura mater closing, and tracheal extubation. Incidences of adverse events were compared using χ^2 tests for the two prespecified comparisons, using a general model (proc genmod) adjusting for the two contrasts. Brain relaxation scores were compared using the Mantel–Haenszel χ^2 test. Absolute changes in biomarker concentrations (differences between induction of anaesthesia and the end of surgery) among the three groups were compared by ANOVA after logarithmic transformation. To adjust for the two specified comparisons (S–F vs. P–R and S–R vs. P–R), *P* values were calculated using the bootstrap technique. Internal consistency for patient satisfaction was measured by Cronbach's α coefficient. Patient satisfaction was evaluated by a score derived from the mean of responses summed for each patient.[18] The two comparisons among anaesthesia groups were performed using the nonparametric two samples Wilcoxon rank sum test.

Results

A total of 411 patients [51% men, mean age 54.8 (SD 13.3) years] were enrolled, with an average of 29 (SD 14) patients (range 6 to 49) enrolled at each participating centre (Fig. 1). Dropouts (7%) are indicated in Fig. 1. Baseline characteristics and preoperative laboratory values were similar among treatment groups. Preoperative diagnoses were also similar among groups [S–F, S–R, P–R ($P = 0.57$)]: malignant neoplasm (78, 68, 82), benign neoplasm (40, 44, 35), and other (18, 24, 21). Mean durations of surgery were similar [$P = 0.06$; 312 (SD 88), 294 (SD 88) and 318 min (SD 95) for S–F, S–R and P–R groups, respectively]. Before tracheal extubation, the mean end-tidal carbon dioxide tension was also similar in the groups [4.53 (SD 1.22), 4.38 (SD 1.51) and 4.43 kPa (SD 1.54) for S–F, S–R and P–R, respectively]. Cumulative doses of the anaesthetics in the three study groups are shown in Table 1.

Fig. 1



Flow diagram of study participants.

Table 1 Doses (mean ± SD) of anaesthetic and analgesic drugs

	Sevoflurane–fentanyl ($n = 130$)	Sevoflurane–remifentanil ($n = 130$)	Propofol–remifentanil ($n = 124$)	$P^{\#}$
Induction				
Propofol (mg)	162.9 ± 45.6	159.6 ± 36.4	156.1 ± 32.0	0.35
Fentanyl (μg)	176.6 ± 58.8			
Remifentanil (μg)		72.1 ± 56.4	66.4 ± 57.0	0.79
Maintenance				
Propofol (mg)			2080.0 ± 860.9	
Fentanyl (μg)	507.8 ± 347.7			
Remifentanil (μg)		2198.5 ± 1167.9	3020.2 ± 1572.5	<0.001

P values are calculated by Student's t-test (two groups) or by analysis of variance (three groups).

Primary outcome

Primary outcome data were available for 380 patients (Table 2). Mean differences and 95% CI were within equivalence limits (−3.0 to 3.0 min) for S–F and P–R [0.20 (−1.62 to 2.63); $P = 0.015$] and for S–R and P–R [−1.43 (−2.83 to 0.40); $P = 0.01$].

Secondary outcomes

Mean baseline heart rate and SBP were similar among the three treatment groups, with a significantly greater decrease in heart rate occurring during surgery among P–R patients ($P < 0.0001$) and a significantly greater decrease in SBP with S–R at dural opening (Fig. 2). At tracheal extubation, heart rate remained lower in the P–R group but SBPs were comparable among all groups (Fig. 2). Between-treatment differences in haemodynamic variables, although statistically significant, were numerically small and not considered clinically relevant. Brain relaxation scores were similar among all groups (Table 2). The use of osmotic diuretics (21% S–F, 22% S–R, and 18% P–R) and hyperventilation (16% S–F, 20% S–R, 20% P–R) were similar. Data on the use of vasoactive drugs were not collected.

Baseline (preanaesthesia) concentrations of all stress biomarkers were within the normal range. Perioperative activation of these biomarkers was attenuated in P–R patients compared with the other two experimental groups (Fig. 3), for instance, the increase in urinary excretion of cortisol was reduced by 73% ($P = 0.0002$) and by 88% ($P < 0.0001$) compared with S–R and S–F patients, respectively. Twenty-four hours after awakening, increases in urinary excretion of cortisol were still significantly higher in the S–R group (0.53 nmol mg^{-1} creatinine, $P = 0.001$) and in the S–F group (0.67 nmol mg^{-1} creatinine, $P = 0.006$) compared with the P–R group (0.20 nmol mg^{-1} creatinine).

Adverse events are summarised in Table 3. During surgery, the only differences were a lower incidence of hypertension and higher incidence of hypotension in the S–R group compared with the P–R group. In all cases, hypertension and hypotension were easily managed by titration of anaesthetic drugs. Shivering was more frequent and nausea and vomiting less frequent in the P–R group. Seizures and postoperative cerebral haematoma were infrequent in all groups, with no group differences. Although differences in incidence of severe postoperative pain between treatments did not reach statistical significance (Table 3), morphine administration during recovery was significantly more frequent among patients who had received remifentanil ($P < 0.0001$). The incidences of postoperative analgesic treatments during the first 24 h with paracetamol, ketoprofen, and morphine were 52.2, 24.3, and 5.2% in the S–R group, 54, 19.7, and 3.7% in the S–F group and 44.9, 15.2, and 22.5% in the P–R group.

Patient satisfaction was recorded for 369 (89.8%) patients. Internal consistency was 0.74 (Cronbach's α) showing good reliability. The median (interquartiles) satisfaction scores were similar: 5.5 (4.8 to 5.8) in the P–R group, 5.4 (4.8 to 5.7) in the S–F group and 5.3 (4.5 to 5.7) in the S–R group. Anaesthetic drug costs were estimated to be €107 for S–F, €131 for S–R and €137 for P–R.

Discussion

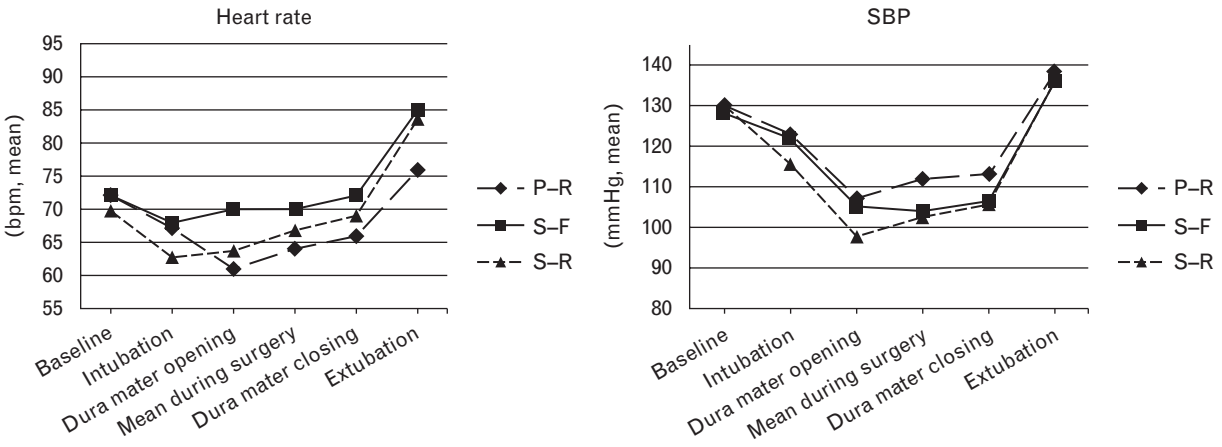
The NeuroMorfeo trial is the largest multicentre and randomised trial to date evaluating anaesthesia for elective craniotomy in patients without intracranial

Table 2 Primary outcome (time to reach Aldrete score ≥9) and brain relaxation

Outcome measure	Sevoflurane-fentanyl	Sevoflurane-remifentanil	Propofol-remifentanil
Time (min) to reach Aldrete score ≥9	($n = 128$)	($n = 130$)	($n = 122$)
Median (IQR)	3.5 (2.0–7.6)	3.3 (1.2–6.5)	3.3 (1.4–8.3)
Brain relaxation score n (%)	($n = 137$)	($n = 136$)	($n = 138$)
Relaxed brain	63 (46.0)	70 (51.5)	73 (52.9)
Mild brain herniation	37 (27.0)	31 (22.8)	35 (25.4)
Moderate herniation without therapy	18 (13.1)	15 (11.0)	13 (9.4)
Severe herniation with therapy	16 (11.7)	16 (11.8)	12 (8.7)

IQR, interquartile range. Between-treatment differences were not statistically significant.

Fig. 2



Between-group effect	*P* value
S–F vs P–R	<0.0001
S–R vs P–R	0.07
Within patients treatment effect: S–F vs P–R	*** *P* value**
Time effect	<0.0001
Time × treatment	<0.0001
Within patients treatment effect: S–R vs P–R	*** *P* value**
Time effect	<0.0001
Time × treatment	<0.0001

Between-group effect	*P* value
S–F vs P–R	<0.002
S–R vs P–R	<0.0001
Within patients treatment effect: S–F vs P–R	*** *P* value**
Time effect	<0.0001
Time × treatment	0.06
Within patients treatment effect: S–R vs P–R	*** *P* value**
Time effect	<0.0001
Time × treatment	0.0002

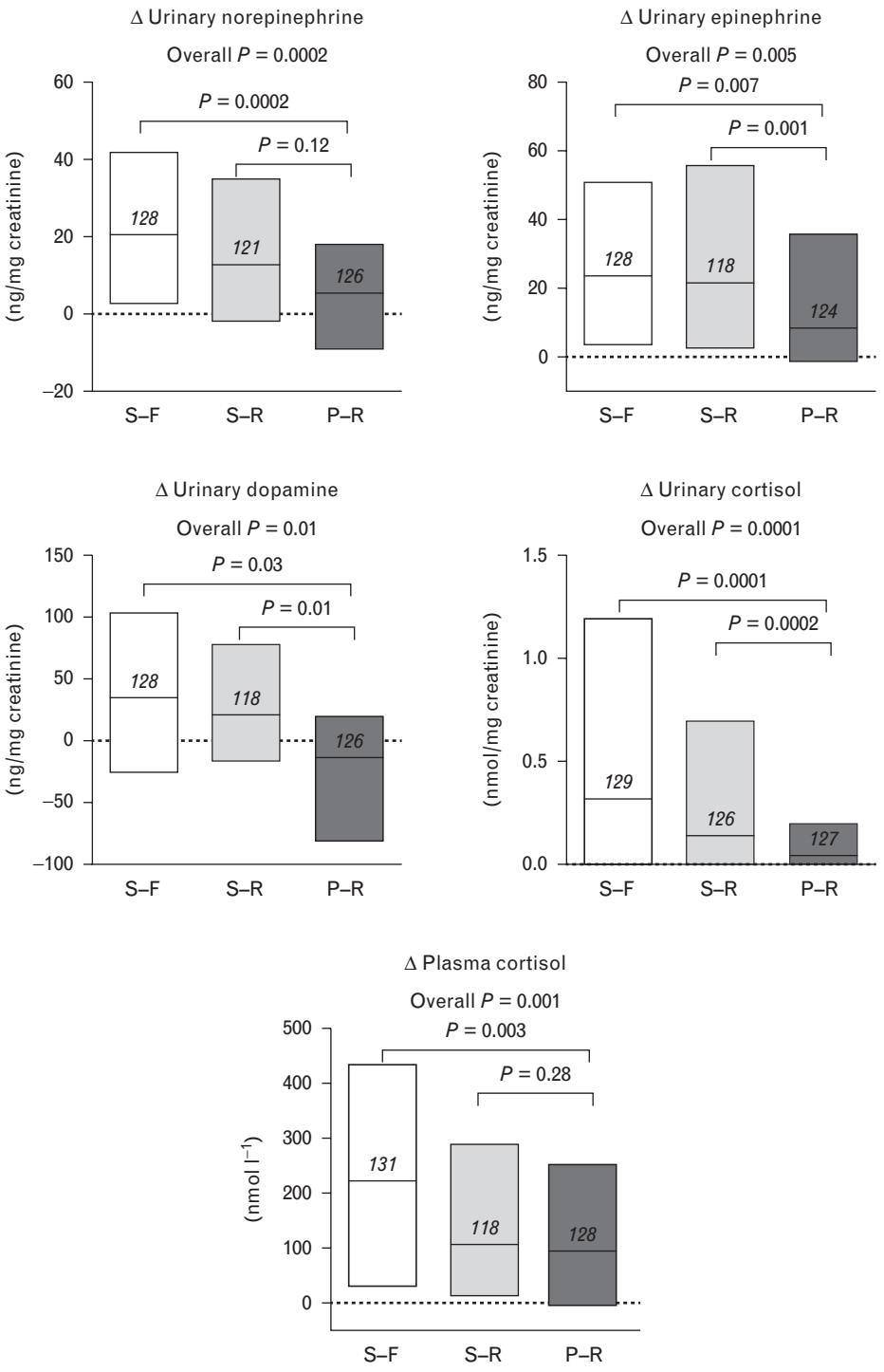
Effects of treatment over time on heart rate and SBP. Heart rate and SBP in the three study groups at fixed observation points (baseline, intubation, dura mater opening, mean value during surgery, dura mater closure, extubation). Treatment effect: results of the univariate repeated measures analysis of variance in 369 patients with complete data available at all time points. **P* values are adjusted Greenhouse-Geisser *P* values. S-F, sevoflurane-fentanyl; S-R, sevoflurane-remifentanil; P-R, propofol-remifentanil.

hypertension. Unlike previous studies, this trial used an equivalence, rather than superiority, design to determine whether inhalational anaesthesia is therapeutically similar to i.v. therapy in respect of postoperative recovery. An equivalence design was selected because previous studies[3–5] have failed to identify clinically significant differences between inhalational and i.v. anaesthesia for elective craniotomy.[8] Secondary endpoints permitted evaluation of potential differences in ancillary, yet potentially clinically important, measures.

For both comparisons (S–R vs. P–R and S–F vs. P–R), the boundaries of the 95% CI for differences were within the prespecified equivalence limits of −3.0 to 3.0 min. Therefore, the null hypothesis of nonequivalence was rejected for both comparisons, and equivalence concluded. Secondary and haemodynamic changes showed statistically significant differences in the incidences of hypertension and hypotension which were not clinically important. Effects of remifentanil (hypotension and bradycardia) were not unanticipated and have been documented previously.[19,20] Patient satisfaction was likewise comparable for inhalational and i.v. anaesthesia.

Urinary catecholamine and cortisol concentrations had lower activation over timein the P–R group. Increased secretion of pituitary and adrenocortical hormones and activation of the sympathetic nervous system are typical of the neuroendocrine stress response to surgery.[21,22] The magnitude of the stress response has been shown previously to be proportional to the severity of injury, the duration of surgery, blood loss and postoperative pain.[23–25] Although anaesthetic strategy may influence perioperative stress responses,[23,26–28] limited information is available on the neuroendocrine stress response during craniotomy except that propofol has been shown to attenuate the surgical stress-induced immune response better than isoflurane.[29] In the current study, intraoperative stress biomarkers were significantly elevated compared with preoperative values. Intravenous anaesthesia was associated with a significant attenuation of the intraoperative neuroendocrine stress response together with a lower heart rate compared with the S–F group, whereas cortisol and catecholamine activation in the S–R group was intermediate. These data compare favourably with previous studies showing blunted perioperative cortisol and catecholamine release with i.v. versus inhalational anaesthesia with sevoflurane for minor elective

Fig. 3



Perioperative changes in neuroendocrine stress response. Plasma and urine samples were collected before induction of anaesthesia and at the end of surgery. Box plots show median and interquartile ranges of changes over time in plasma cortisol concentration and in the urinary excretion of cortisol and catecholamines (all normalised for urinary creatinine concentration) for each experimental group. The ANOVA multitest procedure was used to calculate an overall *P* value among the three experimental groups and *P* values for the predefined comparisons between sevoflurane–fentanyl (S–F) and propofol–remifentanil (P–R), and sevoflurane–remifentanil (S–R) and P–R, groups. The number of patients in each group is indicated in the corresponding box.

Table 3 Adverse events. Data are shown as n (%)

Adverse event	Sevoflurane-fentanyl	Sevoflurane-remifentanil	Propofol-remifentanil	#*P*-value S–F vs. P–R	#*P*-value S–R vs. P–R
During surgery	(*n* = 137)	(*n* = 136)	(*n* = 138)		
Hypotension	30 (21.9)	46 (33.8)	27 (19.6)	0.63	0.009
Hypertension	72 (52.6)	42 (30.9)	66 (47.8)	0.43	0.005
Bradycardia	24 (17.5)	41 (30.2)	42 (30.4)	0.014	0.96
Tachycardia	17 (12.4)	14 (10.3)	7 (5.1)	0.039	0.11
Osmotic diuretic use	29 (21.2)	30 (22.1)	25 (18.1)	0.53	0.42
Hyperventilation	22 (16.1)	27 (19.9)	28 (20.3)	0.37	0.93
Others	7 (5.1)	5 (3.7)	14 (10.1)	0.12	0.045
During recovery	(*n* = 137)	(*n* = 136)	(*n* = 138)		
Cough	2 (1.5)	2 (1.5)	5 (3.6)	0.27	0.28
Shivering	3 (2.2)	9 (6.6)	21 (15.2)	0.001	0.028
Agitation	5 (3.7)	7 (5.2)	9 (6.5)	0.29	0.63
Pain (VAS ≥7)	13 (9.5)	36 (26.5)	24 (17.4)	0.06	0.07
Seizures	1 (0.7)	1 (0.7)	2(1.5)	0.57	0.58
Recovery plus first 24 h after surgery	(*n* = 137)	(*n* = 136)	(*n* = 138)		
Seizures	5 (3.7)	4 (2.9)	6 (4.4)	0.77	0.54
Pain (VAS ≥7)	31 (22.6)	51 (37.5)	37 (26.8)	0.42	0.06
PONV	33 (24.1)	31 (22.8)	12 (8.7)	0.001	0.002
AMI	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Death	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Respiratory insufficiency	0 (0.0)	0 (0.0)	1 (0.7)	NA	NA
Cerebral hematoma	2 (1.5)	1 (0.7)	3 (2.2)	NA	NA

AMI, acute myocardial infarction; NA, not applicable due to low number of occurrences; PONV, postoperative nausea and vomiting; P–R, propofol–remifentanil; S–F, sevoflurane–fentanyl; S–R, sevoflurane–remifentanil; VAS, visual analogue scale. # *P* value from χ^2 test, adjusted for the two comparisons.

otolaryngological[27] and laparoscopic gynaecological procedures.[25] However, benefits from a reduced stress response with P–R may have been offset at the conclusion of anaesthesia by a higher incidence of shivering and pain (based on increased morphine use), suggesting that a different analgesic plan may be required for P–R patients to ensure a smoother emergence from anaesthesia. We aimed to maintain MAP at a target range of 65 to 85 mmHg during surgery and the dose of remifentanil was significantly higher in the P–R group than the S–R group. This may also need to be considered when interpreting differences in stress response among groups.

Interpreting data from this study is limited by the open-label design, although bias was limited for the primary outcome by the PROBE design which maintained blinding to treatment assignment for assessing the primary outcome measure. The PROBE design that permits open-label treatment, which is necessary for delivering anaesthesia, is less costly; more closely mirrors typical clinical practice; and potentially makes the results more clinically applicable, even if it does not completely eliminate the possibility of unblinded operator biases. A meta-analysis reported statistically equivalent outcomes from PROBE and double-blind trials in hypertension supporting the PROBE design.[30]

This study was also limited to patients with normal preoperative consciousness and without signs or symptoms of intracranial hypertension. These data, therefore, cannot be extrapolated to other patient populations, for example more seriously ill patients with intracranial hypertension or patients requiring nonelective surgery. The Aldrete score may not be a particularly sensitive quality of outcome measure but was selected for this study because it is widely used in both research and clinical practice. Haemodynamic management is an important part of neurosurgical care and outcome after craniotomy. Unfortunately, this study did not capture haemodynamic events or the use of vasoactive drugs during recovery. Depth of anaesthesia monitoring was not included in this study. Such monitoring might provide additional support for a particular treatment and should perhaps be included in future studies. Finally, decreases in the stress response in the P–R group may have resulted in benefits that were not captured during the initial postoperative day. Future studies may wish to evaluate longer-term clinical outcomes to assess the potential impact from intraoperative stress response attenuation.

In conclusion, the NeuroMorfeo trial has demonstrated equivalence in time to awakening from anaesthesia when comparing inhalational anaesthesia with i.v. anaesthesia for elective craniotomy in patients without intracranial hypertension. Secondary outcomes generally supported equivalence between treatments, with the exceptions of a blunting of the endocrine stress response and increases in postoperative pain and shivering with i.v. anaesthesia.

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This report describes human research. Institutional Review Board (IRB) contact information: Comitato Etico, Azienda Ospedaliera San Gerardo di Monza Tel. 039/2333693; E-mail: comitato.etico@hsgerardo.org. Secretary: Michela Melchiorre.

This study was conducted with written informed consent from the study subjects.

This report describes a prospective randomised clinical trial. The authors state that the report includes every item in the CONSORT checklist for a prospective randomised clinical trial.

Assistance with the study: the study design was discussed and defined with The NeuroMorfeo Study Group. The composition of the group is as follows:

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