Brief Reports

Does intrathecal morphine alter the stress response following coronary artery bypass grafting surgery?

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Purpose: Intrathecal morphine administered prior to coronary artery revascularization (CABG) surgery was studied to determine its effects on the stress response.

Methods: In a single centre, open, randomized clinical trial, first time elective CABG surgery patients, < 75 yr, were studied. Control subjects (n=12) received a standardized anesthetic consisting of fentanyl (maximum cumulative dose of 35 $\mu\text{g}\cdot\text{kg}^{-1}$), propofol, and pancuronium. In addition, spinal subjects (n=13) received 1.0 mg (age > 60 yr) or 1.5 mg (age $\leq$ 59 yr) intrathecal morphine prior to induction of anesthesia. Control subjects received continuous *iv* morphine at 2 $\text{mg}\cdot\text{hr}^{-1}$ on arrival in the ICU with *iv* bolus morphine supplementation as required while spinal subjects received bolus *iv* morphine as required. Changes in plasma cortisol and catecholamine concentrations were measured preoperatively, poststernotomy, on admission to ICU, following tracheal extubation, at 0800 hr on the first postoperative day, and 24 and 48 hr after ICU admission.

Results: No differences between groups were detected for demographic variables. The percent change in cortisol concentration relative to preoperative values (control vs spinal; (38 (87) vs -41 (46)%: $P < 0.05$)) was lower in the spinal group on admission to ICU. The percent change in plasma epinephrine levels (control vs spinal) on admission to ICU (285 (337) vs -10 (37)%) and 0800 hr after surgery (314 (341) vs -4 (37)%) was also significantly different.

Conclusion: Intrathecal morphine only partially attenuated the postsurgical stress response in CABG surgical patients.

Objectif : L'administration intrathécale de morphine, antérieure au pontage aortocoronarien, a été étudiée afin de déterminer ses effets sur la réponse au stress.

Méthode : L'essai clinique randomisé et ouvert a eu lieu dans un seul centre auprès de patients < 75 ans qui subissaient un premier pontage planifié. Les sujets témoins (n=12) ont reçu une anesthésie standard qui comprenait du fentanyl (dose cumulative maximale de 35 $\mu\text{g}\cdot\text{kg}^{-1}$), du propofol et du pancuronium. Les sujets sous rachianesthésie (n=13) ont reçu en plus 1,0 mg (> 60 ans) ou 1,5 mg ($\leq$ 59 ans) de morphine intrathécale avant l'induction de l'anesthésie. Les témoins ont reçu une perfusion *iv* continue de morphine à 2 $\text{mg}\cdot\text{h}^{-1}$ à l'arrivée à l'USI et des bolus *iv* de morphine supplémentaire au besoin, alors que les autres sujets ont reçu des bolus *iv* de morphine au besoin. Les changements de concentrations plasmatiques de cortisol et de catécholamine ont été mesurés avant l'intervention, après la sternotomie, à l'admission à l'USI, après l'extubation trachéale, à 8 h le premier jour postopératoire et à 24 et 48 h après l'admission à l'USI.

Résultats : Aucune différence intergroupe n'est apparue quant aux variables démographiques. Le taux de changement de la concentration de cortisol relative aux valeurs préopératoires (témoin vs rachianesthésie; (38 (87) vs -41 (46) % : $P < 0,05$)) a été plus bas dans le groupe sous rachianesthésie lors de l'admission à l'USI. Le taux de changement des niveaux d'épinéphrine plasmatique (témoin vs rachianesthésie) à l'admission à l'USI (285 (337) vs -10 (37) %) et à 8 h après l'opération (314 (341) vs -4 (37) %) était aussi significativement différent.

Conclusion : L'administration intrathécale de morphine atténue seulement de façon partielle la réponse au stress postchirurgical chez des patients qui subissent un pontage aortocoronarien.

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Accepted for publication February 2, 2000.

ATTENTION has focused recently on the ability of anesthetic agents, administered during cardiac surgery, to ameliorate the stress response.¹ Neuraxial opioids may reduce hormonal and adrenergic responses to stress.^{2,3} A positive correlation between plasma concentrations of catecholamines and other stress responding hormones (e.g. cortisol) and the depth of anesthesia employing intravenous opioids as a component of the anesthetic mix has been demonstrated.⁴ However, use of intrathecal opioids to ameliorate the stress response following cardiac surgery has been restricted due to concerns regarding respiratory depression⁵ and coagulopathy-induced spinal cord compression.⁶

Methods

Following institutional review and approval and informed consent, patients undergoing first time elective coronary artery revascularization surgery with no contraindication to neuraxial injection were studied. After arrival in the operating room, patients were randomly assigned to one of two groups (spinal *vs* control) in a 1:1 ratio.

Patients in the intrathecal morphine group <60 yr received 1.5 mg and > 60 yr received 1 mg morphine intrathecally. Induction of anesthesia was with fentanyl up to 10-15 $\mu\text{g}\cdot\text{kg}^{-1}$, propofol up to 2 $\text{mg}\cdot\text{kg}^{-1}$ and pancuronium 0.1 $\text{mg}\cdot\text{kg}^{-1}$ for muscle relaxation. Following tracheal intubation, anesthesia was maintained via a propofol infusion at 50-200 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, supplemented by fentanyl to a maximum of 35 $\mu\text{g}\cdot\text{kg}^{-1}$ cumulative dose to maintain mean arterial blood pres-

sure and heart rate within $\pm 20\%$ of the baseline value obtained at the preoperative visit.

In the ICU, subjects in the control group received 2 $\text{mg}\cdot\text{hr}^{-1}$ morphine by continuous *iv* infusion with additional bolus morphine in amounts of 2 mg as necessary. Subjects in the spinal group received a 2 mg morphine *iv* bolus when needed for breakthrough pain. Sedation, if required, was provided using propofol.

Stress response was determined by changes in plasma cortisol and catecholamine concentrations. Blood was collected at seven intervals: preoperatively; post-sternotomy; admission to the ICU; at the time of extubation; 0800 hr of the first postoperative day; and at 24 and 48 hr after admission to the ICU. These times were based on likely physiological responses over time and economic limitations.

Catecholamine Analysis: Plasma catecholamine levels were determined using a modification of the methodology of Weicker *et al.*⁷ The sensitivity ($\text{pg}\cdot\text{ml}^{-1}$) and coefficient of variation (%) for epinephrine was 8 $\text{pg}\cdot\text{ml}^{-1}$ and 17%, for norepinephrine 6 $\text{pg}\cdot\text{ml}^{-1}$ and 14%, and for dopamine 6 $\text{pg}\cdot\text{ml}^{-1}$ and 17%.

Plasma Cortisol Analysis: Plasma cortisol levels were determined using a radioimmunoassay technique (Gamma Coat® Cortisol ¹²⁵IRIA). The sensitivity was 0.2 $\mu\text{g}\cdot\text{dl}^{-1}$ (0.6 $\text{nmol}\cdot\text{dl}^{-1}$) and coefficient of variation was 9%.

For repeated measurements, differences between groups for catecholamine and cortisol levels were analyzed using repeated measures ANOVA. Any test statistic reported as significant was then analyzed *post hoc* using the Bonferroni t test.

TABLE I Patient demographics (Results are expressed as mean $\pm$ SD).

	Control (n=12)	Spinal (n=13)	p Value
Sex (F/M)	1/11	1/12	0.953
Age (yr)	59.5 $\pm$ 8.2	61.8 $\pm$ 8.1	0.481
Height (cm)	173.2 $\pm$ 6.8	160.1 $\pm$ 27.7	0.108
Weight (kg)	86.7 $\pm$ 8.1	97.3 $\pm$ 2.7	0.18
MI	7	7	0.870
Smoker	7	13	0.047
Diabetes	4	3	0.294
ASA II/III/IV	3/6/3	1/6/6	0.357
Intraoperative:			
Anesthesia time (min)	319 $\pm$ 51	324 $\pm$ 43	0.770
CPB time (min)	113 $\pm$ 32	110 $\pm$ 38	0.83
Vasopressor use (n)	3	18	0.000
Propofol ($\text{mg}\cdot\text{kg}^{-1}$)	21 $\pm$ 8	20 $\pm$ 6	0.880
Fentanyl ($\mu\text{g}\cdot\text{kg}^{-1}$)	36 $\pm$ 8	32 $\pm$ 7	0.785

F = female, M = male, MI = myocardial infarction, ASA = American Society of Anesthesiologists classification of physical status.

FIGURE 1 Visual analogue score (VAS) *vs* time in the ICU.

TABLE II Mean concentration of stress markers. (Results are mean $\pm$ SD).

	PREOP	POST STERN	ICU ADMIT	EXTUBATE	0800 hr POSTOP	24 hr AFTER	48 hr AFTER
EPI							
C	103 $\pm$ 83	184 $\pm$ 105	257 $\pm$ 161	436 $\pm$ 476	279 $\pm$ 175	384 $\pm$ 389	275 $\pm$ 163
S	210 $\pm$ 87	114 $\pm$ 42	191 $\pm$ 119	224 $\pm$ 158	202 $\pm$ 122	278 $\pm$ 308	298 $\pm$ 344
NE*							
C	444 $\pm$ 351	905 $\pm$ 805	941 $\pm$ 996	1027 $\pm$ 457	956 $\pm$ 455	1305 $\pm$ 1170	1400 $\pm$ 1233
S	453 $\pm$ 218	487 $\pm$ 292	454 $\pm$ 447	834 $\pm$ 792	582 $\pm$ 505	668 $\pm$ 628	877 $\pm$ 687
DA							
C	670 $\pm$ 1165	559 $\pm$ 710	295 $\pm$ 274	558 $\pm$ 847	493 $\pm$ 894	427 $\pm$ 336	219 $\pm$ 138
S	265 $\pm$ 269	296 $\pm$ 635	659 $\pm$ 1160	361 $\pm$ 449	318 $\pm$ 499	424 $\pm$ 543	288 $\pm$ 462
COR*							
C	406 $\pm$ 141	284 $\pm$ 205	506 $\pm$ 333	1268 $\pm$ 226	691 $\pm$ 214	795 $\pm$ 281	601 $\pm$ 258
S	371 $\pm$ 90	228 $\pm$ 77	207 $\pm$ 140†	905 $\pm$ 315†	755 $\pm$ 234	734 $\pm$ 305	542 $\pm$ 235

concentration of catecholamines = pg·mL⁻¹; concentration of cortisol = nmol·L⁻¹

*NE; $P = 0.034$: post hoc analysis failed to identify specific time point;

COR: $P = 0.027$: † $P < 0.05$ *vs* control

EPI= epinephrine, NE=norepinephrine, DA=dopamine, COR=cortisol, PREOP=preoperative, POST STERN=post sternotomy, ICU ADMIT=intensive care unit admission, 0800 hr=0800 hr after admission to ICU, 24 hr AFTER=24h after admission to ICU, 48 hr=48 hr after admission to ICU.

Differences between groups for continuous variables were analyzed using a t test and for discrete variables using Fisher's exact test or chi square analysis.

Results

Demographics for the patients are shown in Table I. The spinal group received more intraoperative vasopressors such as ephedrine and phenylephrine to support the blood pressure. The total intraoperative dose of fentanyl was not different between groups.

Eleven patients enrolled in the spinal group received very little additional analgesics and two required additional analgesics at rates similar to the control group (data not shown). The reported pain level was consistently higher in control patients (Figure 1).

Excluding values from patients receiving exogenous dopamine as inotropic support ($n=2$ in each group), the mean plasma concentrations of epinephrine and dopamine in control *vs* spinal treated patients did not differ. Plasma levels of norepinephrine in the spinal group were significantly different from the control group. The plasma levels of cortisol in spinal treated patients were lower than in control patients on admission to the ICU and at the time of tracheal extubation (Table II).

When examined as percent change from baseline, epinephrine levels were lower in the spinal group on admission to the ICU and 0800 hr after surgery and for cortisol on admission to ICU ($P < 0.05$) (Figure 2).

Discussion

In keeping with the findings of Chaney *et al.*³ (who used substantially higher doses of intrathecal morphine), in this study the use of intrathecal morphine as a component of the anesthetic mixture for CABG surgery was associated with a partial reduction in the stress response as measured by change in plasma cortisol and catecholamine levels. Use of intrathecal morphine required more vasopressor support to maintain stable intraoperative hemodynamics but improved postoperative analgesia, with reduced supplemental analgesic requirements.

During cardiac surgery, activation of the sympathetic nervous system occurs in response to noxious stimuli.⁸ By blunting the response to noxious stimulation, opioids may have a role to play in ameliorating the stress response^{1,3,4,8,9} but this has been difficult to demonstrate using intrathecal morphine in adults.³

Why might intrathecal opioids fail to completely ameliorate the stress response during cardiac surgery? Catecholamines and other stress hormones may be released by factors other than noxious stimulation e.g. activation of the cytokine network.¹ Alternatively, activation of the stress response by noxious stimulation may occur before adequate intrathecal levels of morphine are reached. Support for this hypothesis is provided in this study. Doses of intraoperative fentanyl required to maintain hemodynamic stability were similar between

FIGURE 2 Percent changes in stress hormone levels. Panel A Norepinephrine; Panel B Epinephrine; Panel C Dopamine; Panel D Cortisol.

Significant differences were detected for epinephrine and cortisol changes over time between groups.

the two groups. The periods of maximum stimuli (e.g. intubation, incision, sternotomy) occur early in the

course of surgery and perhaps before adequate levels of intrathecal morphine are achieved (peak onset of activity approximately six hours).^{5,10} To blunt noxious stimulation occurring at these times, the same amount of intravenous fentanyl would be required whether patients received intrathecal morphine or not. As concentrations of intrathecal morphine increased, this would have a synergistic effect with the previously administered intravenous opioid (hence requirements for more vasoactive agents later on in the course of surgery as occurred in our study) and superior analgesia in the ICU (better VAS score).

In summary, this study demonstrated that intrathecal morphine only partially ameliorated the stress response to cardiac surgery.

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