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Opioid sedation does not alter intracranial pressure in head injured patients

Purpose: This study aimed to examine the effects of sedative doses of morphine, fentanyl and sufentanil on intracranial pressure (ICP) in head-injured patients in whom changes in mean arterial pressure (MAP) were minimized.

Methods: Fifteen severely head-injured patients (GSC of ≤ 8) were randomly assigned to receive either fentanyl, sufentanil or morphine, titrating the drug to a maximal 10% decrease in MAP. The patients were subsequently given an infusion of the same opioid. For four hours, ICP, MAP and heart rate were recorded.

Results: In all groups, there were no increases in ICP. There was a decrease in MAP in the sufentanil group at 10 min ($P < 0.05$) and 45 min after the initial opioid bolus. These decreases in MAP were not associated with increases in ICP.

Conclusion: The study suggests that when opioids are titrated in head-injured patients, worsening intracranial pressure can be avoided.

Objectif : Étudier les effets de doses sédatives de morphine, de fentanyl et de sufentanil sur la pression intracrânienne (PIC) chez des traumatisés du crâne dont la pression artérielle moyenne (PAM) n'avait que légèrement varié.

Méthodes : Quinze graves traumatisés du crâne (Échelle de Glasgow ≤ 8) ont été assignés aléatoirement pour recevoir du fentanyl, du sufentanil, ou de la morphine titrés de façon à abaisser la PAM de 10% ou moins. Les patients ont par la suite reçu une perfusion du même morphinique. Pendant quatre heures, la PIC, la PAM et la fréquence cardiaque étaient enregistrées.

Résultats : La PIC est demeurée inchangée dans tous les groupes. La PAM a baissé dans le groupe sufentanil à la 10^e minute ($P > 0,05$) et à la 45^e minute qui ont suivi l'administration du bolus initial. Ces diminutions de la PAM n'étaient pas associées à une augmentation de la PIC.

Conclusion : Cette étude suggère que l'administration titrée de morphiniques à des traumatisés du crâne ne provoque pas de détérioration de la pression intracrânienne.

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OPIOID receptor agonists, including the synthetic opioids fentanyl and sufentanil, are frequently used as anaesthetic adjuncts during the perioperative management of neurosurgical patients. Previous studies have documented that agonists decrease the requirements for volatile anesthetic agents.¹⁻³ The volatile anaesthetic agents produce direct cerebral vascular dilatation, resulting in an increase in cerebral blood volume (CBV), and potentially increasing intracranial pressure (ICP). In contrast, opioid agonists are associated with preservation of cerebral vascular autoregulatory responses to changes in PCO_2 and mean arterial pressure (MAP).^{4,8}

Recent studies have questioned the use of opioids in patients with compromised intracranial compliance. Milde *et al.*⁵ demonstrated an increase in cerebral blood flow (CBF) and ICP after the administration of sufentanil to normal dogs. Since this initial study, other conflicting studies in humans and animals have followed.⁶⁻¹³ Sperry *et al.*¹⁴ administered bolus injections of fentanyl ($3 \mu\text{g}\cdot\text{kg}^{-1}$) or sufentanil ($0.6 \mu\text{g}\cdot\text{kg}^{-1}$) in sedative doses to head-injured patients. The administration of either fentanyl or sufentanil was associated with increases in ICP and decreases in systemic MAP of >10%. The increase in ICP returned to baseline after 30 min. A similar study was performed by Albanese *et al.*¹⁵ in which a sufentanil bolus of $1 \mu\text{g}\cdot\text{kg}^{-1}$ followed by $0.005 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ infusion was associated with decreases in systemic MAP and increases in ICP.

The purpose of the present investigation was to compare the effects of fentanyl, sufentanil or morphine sedation on alterations in the ICP of head-injured patients while attempting to maintain MAP.

Methods

After institutional and human research committee approval, 15 severely head-injured patients were randomized to receive either morphine (Group 1, $n=5$), fentanyl (Group 2, $n=5$), or sufentanil (Group 3, $n=5$) for sedation. Before this study, morphine had been used as the sole opioid in the intensive care unit, and was considered the control agent for study comparison.

Patient selection

All patients were haemodynamically stable and had been without pharmacological pressor support for two hours before initiation of the study. Patients who were pregnant, were <16 yr of age, were morbidly obese or had any pre-existent neurological, cardiac, renal or hepatic disease before their head injury were excluded from the study. In our institution, ICP monitoring is reserved for those patients who were head injured, yet

failed diuretics and hyperventilation. In all patients, the tracheas were intubated, the lungs mechanically ventilated and hyperventilated to $PaCO_2$ of 25–30 mmHg as determined by arterial blood gas determination. The lungs were ventilated with a Servo ventilator (Siemens Corporation). All patients had been receiving phenytoin $2 \text{ mg}\cdot\text{kg}^{-1}$ q8h, ranitidine or cimetidine (50 mg or 300 mg q8h, respectively, for stress ulcer prophylaxis), midazolam ($2\text{--}5 \text{ mg}\cdot\text{hr}^{-1}$), and mannitol ($0.5\text{--}2.0 \text{ g}\cdot\text{kg}^{-1}$, to maintain serum osmolality 300–320 mOsm $\cdot\text{kg}^{-1}$). All patients were kept in a 20 head-up position. No patients had received morphine for two hours prior to the initiation of this study. No patients were receiving muscle relaxants at the time of the study.

Monitoring

All patients were monitored with continuous electrocardiography (Leads II, and modified V_5) (Marquette Electronics, Milwaukee, WI), pulse oximetry (Ohmeda Corporation, Madison, WI), and intermittent temperature measurements. All patients had indwelling radial artery catheters for direct arterial pressure measurements. All patients had subdural ICP monitors placed electively under local anaesthesia (lidocaine 1%) by neurosurgeons in the intensive care unit before the initiation of the study. The ICP monitoring system was a Camino subdural catheter (OLM Intracranial Pressure Monitor, Camino Laboratories, San Diego, CA) coupled to a Marquette Series 7000 monitor via a dual pressure Marquette module (Marquette Electronics, Milwaukee WI). The Camino catheter system uses a subarachnoid bolt and miniature ICP transducer.

Clinical protocol

In all groups, an opioid loading dose was administered by timed, slow, continuous intravenous administration over a five minute interval. The infusion was continuously adjusted to a targeted alteration in systemic mean arterial pressure of not more than 5% from preinfusion control value. If the blood pressure changed by 5% from the control value, the opioid infusion was stopped. This dose was subsequently calculated in terms of a $\text{mg}\cdot\text{kg}^{-1}$ dose for morphine, or $\mu\text{g}\cdot\text{kg}^{-1}$ dose for fentanyl or sufentanil. This dose was then used as the basis to initiate a continuous infusion which was maintained for four hours. During this time, ICP, MAP, and heart rate were continuously monitored and recorded every 15 min for the first two hours, and then every 30 min for the last two hours of the study. Cerebral perfusion pressure (CPP) was calculated as (MAP-ICP) for all the data points available.

Statistical analysis

Data within and between groups before and during drug administration were analyzed with a repeated measures analysis of variance (ANOVA) followed by application of Bonferroni-adjusted paired *t* tests. Changes from control within a condition or between conditions were considered statistically significant when *P* was < 0.05. The SAS software package was utilized for statistical analysis. ANOVA was used to analyze differences in demographic data. All data are expressed as means $\pm$ standard error of the mean. Analysis of relationship between MAP and ICP was performed with both a Spearman Rank Order Correlation and Pearson Product Correlation using Sigma Stat statistical software.

Results

Demographic data

Patient age ranged from 16 to 52 yr. All three groups had Glasgow Coma Scale scores representing severe head trauma (GCS < 8). All patients had PCO₂ values between 26 and 29 mmHg. There were no differences between groups except for weight, with the sufentanil group being slightly heavier (ANOVA, *P*=0.05) (Table 1).

Haemodynamic and icp response to opioids

The mean doses of fentanyl, morphine and sufentanil in each group are listed in Table II. The average initial bolus doses were $2.98 \pm 1.73 \mu\text{g}\cdot\text{kg}^{-1}$ for the fentanyl group, $0.07 \pm 0.03 \text{ mg}\cdot\text{kg}^{-1}$ for the morphine group, and $0.37 \pm 0.13 \mu\text{g}\cdot\text{kg}^{-1}$ for the sufentanil group.

Baseline MAP in the three groups was not different (morphine 90.8 ± 6.9 mmHg, fentanyl 90.8 ± 4 mmHg, sufentanil 98.4 ± 5.8 mmHg, *P* < 0.05). The recorded MAPs during this study were not different

from baseline throughout the four hour study period except in the sufentanil group at 10 min (mean 80.6 ± 12.1 mmHg, *P* < 0.05) and 45 min after bolus administration (mean 82.4 ± 8.8). (Figure 1) The MAP was lower than baseline at these times.

Baseline ICPs were not different among groups (morphine 14.6 ± 5 mmHg, fentanyl 13.6 ± 3 mmHg, sufentanil 18.2 ± 3). In addition, the ICPs did not change from baseline in any group. The fentanyl-sedated patients had reduced ICP at 150 and 180 min compared with the morphine- and sufentanil-sedated patients. (Figure 2).

Cerebral perfusion pressure was not different from baseline in any of the three groups. The fentanyl patients had a lower CPP than morphine at 60 minutes, and was statistically lower than both morphine and sufentanil at 75 minutes (Figure 3).

FIGURE 1 The effect of morphine, fentanyl or sufentanil sedation on mean arterial pressure (values are mean $\pm$ SEM).

* = statistically different from baseline control (*P* < 0.05)

FIGURE 2 The effect of morphine, fentanyl or sufentanil sedation on mean intracranial pressure.

+ = statistically different from both morphine and sufentanil (*P* < 0.05)

TABLE I Demographic Data

	Morphine	Fentanyl	Sufentanil
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Age (yr)	21 $\pm$ 6	22 $\pm$ 9	35 $\pm$ 12
Glasgow Coma Score	6 $\pm$ 2	5 $\pm$ 2	6 $\pm$ 2
Weight (kg)	73 $\pm$ 6	59 $\pm$ 12	84 $\pm$ 21
PCO ₂	28 $\pm$ 1	26 $\pm$ 4	29 $\pm$ 2
pH (range)	7.45–7.56	7.49–7.58	7.49–7.51

TABLE II Opioid Doses Administered to ICP Patients (Mean $\pm$ SD)

	Bolus	Infusion
Fentanyl	$2.98 \pm 1.73 \mu\text{g}\cdot\text{kg}^{-1}$	$1.63 \pm 0.48 \mu\text{g}\cdot\text{kg}/\text{h}^{-1}$
Morphine	$0.07 \pm 0.03 \text{ mg}\cdot\text{kg}^{-1}$	$0.03 \pm 0.02 \text{ mg}\cdot\text{kg}/\text{h}^{-1}$
Sufentanil	$0.37 \pm 0.13 \mu\text{g}\cdot\text{kg}^{-1}$	$0.33 \pm 0.16 \mu\text{g}\cdot\text{kg}/\text{h}^{-1}$

FIGURE 3 The effect of morphine, fentanyl or sufentanil sedation on cerebral perfusion pressure

* = statistically different from morphine

† = statistically different from morphine and sufentanil

The relationship between ICP and MAP was analyzed by Spearman Rank Order correlation and Pearson Product Moment correlation. There was no relationship between ICP and MAP in the patients sedated with morphine. Both fentanyl and sufentanil demonstrated a positive correlation, meaning both variables increased together (Figure 4) ($P < 0.01$).

Baseline heart rates were not different. Heart rates were lower in the sufentanil group than in the fentanyl groups at all times except baseline and at 75 min and were different from morphine at 105, 120, 180 and 240 min.

Discussion

In the present investigation, changes in systemic MAP for each patient were minimized in order to examine the effect of a sedative dose of opioid on ICP alterations in patients with pre-existing elevation of ICP. The initial sedative dose was determined by a maximal 5% decrease in systemic MAP. The patients were then given an opioid infusion, with the dose calculated from the sedative amount that just resulted in this alteration in systemic MAP. The results demonstrate no increases in ICP in the morphine, fentanyl or sufentanil groups.

This study was designed to maintain MAP close to baseline. This was accomplished in all but the sufentanil group in which at 10 and 45 min post-bolus the MAP decreased below baseline. The magnitude of the changes of MAP were small, but when related to the alterations in ICP, there was a tendency for an increase or decrease in MAP to be met with the same change in ICP in the fentanyl and sufentanil sedated patients. This is in conflict with other studies of opioids^{6,14-16,25,26} when the administration of opioids

caused a decrease in MAP which was met with an increase in ICP. Werner *et al.*,²⁴ for example, developed worsened ICP in patients given sufentanil if their MAP decreased >10 mmHg. In his study, the baseline ICP levels were low (< 3), but this study had patients with Glasgow Coma Scales of < 6 . In these studies, the range of baseline ICPs were between 0–12 mmHg (in those that reported their baseline ICP) with the exception of the study by Albanese.¹⁵

Bouma *et al.*¹⁸ evaluated intracranial dynamics with CBF measurement and intraventricular compliance evaluations from intraventricular catheters, and two groups of patients emerged. Patients without intact autoregulation had intracranial pressures that varied directly with MAP. The other group, patients with intact autoregulation, developed large increases in ICP with modest lowering of MAP, though an increase in MAP did not necessarily increase ICP. Perhaps patients with lower baseline ICPs, as in these studies, maintain autoregulation better. Weinstable²² had a group of patients with ICPs of ≥ 20 mmHg and did not find elevations of ICP in response to decreases in MAP when given sufentanil. In our study, the baseline ICPs were higher, and loss of autoregulation is consistent with the overall relationship of MAP and ICP changes reported in this study.

The maintenance of MAP could have been accomplished by pressor agents. In the present investigation, pressor agents were not used to maintain systemic MAP. In a study by Mayberg *et al.*,¹⁶ when MAP was supported by phenylephrine, the increase in ICP associated with the administration of alfentanil was ameliorated. Here, no pressor agents were utilized in order to evaluate the effects of the opioid agonists on ICP independently.

Minute ventilation was kept constant to maintain hypocarbia. Whether the use of hyperventilation worsened or improved ICP in this study is unknown as there was no prehyperventilation baseline with which to compare it. Previous studies that evaluated the effect of opioids on ICP varied in the use of hyperventilation. The patients were not standardized to receive nondepolarizing muscle relaxants. It is our preference to be able to continually follow patients with neurological examinations.

The average dose of fentanyl used in this study ($3 \pm 1.7 \mu\text{g}\cdot\text{kg}^{-1}$) was similar in magnitude to the double-blind bolus ($3 \mu\text{g}\cdot\text{kg}^{-1}$) given to head-injured patients by Sperry *et al.*¹⁴ The average dose of sufentanil in our study was $0.38 \pm 1.3 \mu\text{g}\cdot\text{kg}^{-1}$ whereas Sperry *et al.* administered $0.6 \mu\text{g}\cdot\text{kg}^{-1}$ sufentanil. All patients received individualized, not uniform, doses of opioids to control systemic MAP. Varying the dose of opioids to a physiological target endpoint is, in general, the clinical paradigm most commonly employed. However, the endpoint in a head-

injured population in which the patients' tracheas are intubated and their lungs mechanically ventilated is not precise. In the current investigation, the target endpoint was a < 5% change in MAP. In a recent study, it was demonstrated that sufentanil, at a lower dose than that used on our study ($0.1 \mu\text{g}\cdot\text{kg}^{-1}$), combined with hyperventilation, induced a decrease in spectral EEG power into the delta range.²¹ Consequently, a $0.38 \mu\text{g}\cdot\text{kg}^{-1}$ sufentanil should have been an adequate sedative dose.

In summary, the present investigation suggests that slow titrated administration of fentanyl, sufentanil or morphine with subsequent continued infusion preserves systemic arterial pressure without elevating ICP.

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