Effect of remifentanil on intracranial pressure and cerebral blood flow velocity in patients with head trauma

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Background: Remifentanil, an ultra-short-acting opioid, is used as an on-top analgesic in head trauma patients during transient painful procedures, e.g. endotracheal suctioning, physiotherapy, on the intensive care unit. However, previous studies have shown that opioids may increase intracranial pressure and decrease cerebral blood flow.

Methods: The present study investigates the effect of remifentanil on mean arterial blood pressure, intracranial pressure measured with intraparenchymal or epidural probes, and on cerebral blood flow velocity assessed by transcranial Doppler flowmetry in 20 head trauma patients sedated with propofol and sufentanil. Ventilation was adjusted for a target PaCO₂ of 4.7–5.1 kPa. After baseline measurements a bolus of remifentanil (0.5 μg·kg⁻¹ i.v.) was administrated followed by a continuous infusion of remifentanil (0.25 μg·kg⁻¹·min⁻¹ i.v.) for 20 min.

Results: There was no change in mean arterial blood pressure, intracranial pressure, and cerebral blood flow velocity in response to remifentanil infusion over time. Statistical analysis was performed using the Wilcoxon Signed Rank test.

Conclusions: These data suggest that remifentanil can be used for on-top analgesia in head trauma patients without adverse effects on cerebrovascular haemodynamics, cerebral perfusion pressure or intracranial pressure.

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Key words: Cerebral blood flow velocity; head trauma; intracranial pressure; remifentanil.

In patients with head trauma sedation using hypnotic and narcotic agents is performed to reduce stress and to control intracranial pressure (ICP<20 mmHg). Likewise, sedation should be tapered to obtain access to the patient for repetitive assessments of neurologic function. Therefore, the depth of background sedation/analgesia of the patient may be inadequate during painful stimuli such as endotracheal suctioning, physiotherapy, or minor surgical interventions with concomitant increases in ICP, decreases in cerebral perfusion pressure (CPP) and jugular bulb oxygen saturation (1). Remifentanil is a potent μ-receptor agonist with a short context-sensitive half-life, which allows for perfect titration of the analgesic effect (2, 3). This makes remifentanil a potent supplement for analgesia during painful manipulations of short duration. However, previous studies have shown that opioids increase ICP and decrease cerebral blood flow (CBF) (4–6). The present study investigates the effect of remifentanil on ICP and cerebral blood flow velocity (CBFV) in patients with head trauma.

Methods

After approval of the Institutional Research Ethics Committee to perform the study without informed consent, 20 consecutive patients with traumatic brain injury (Glasgow Coma Scale <8) were studied between days 2 and 6 after admission to the intensive care unit. Mechanical ventilation (FiO₂=0.3–0.5) was adjusted to maintain PaCO₂ at 4.7–5.1 kPa. Deep sedation was performed with a continuous infusion of propofol and sufentanil i.v. (Table 1) for a period of 24 h before investigation. Mean arterial blood pressure (MAP) was maintained above 80 mmHg using norepinephrine, epinephrine, or dopamine infusion. After baseline measurements the concentrations of all drugs were kept constant. Invasive MAP and heart rate (HR) were monitored continuously. Intracranial pressure was measured using an epidural (Spiegelberg, Hamburg, Germany) or an intraparenchymal probe (Codman Micro-Sensor ICP Transducer; Codman & Shurtleff, Inc, Raynham, MA). Cerebral blood
flow cerebral artery by transtemporal approach using a 2-MHz transcranial Doppler system (TCD, Multidop P, DWL, Sipplingen, Germany). In patients with unilateral injury (according to cerebral computer-tomography) CBFV was measured in the contralateral hemisphere, while in patients with global damage the less injured hemisphere was chosen for monitoring. To ensure constant angles and depth of insonation the TCD-probe was fixed using a specially designed frame during the entire study.

After assessing baseline data a bolus of remifentanil (0.5 μg·kg⁻¹ i.v.) was administered followed by a continuous infusion of remifentanil (0.25 μg·kg⁻¹·min⁻¹ i.v.) for 20 min (Fig. 1). The parameters MAP, ICP, CPP, and CBFV were monitored at baseline (T1), 1 min (T2), 5 min (T3), and 20 min (T4) after the start of the remifentanil administration, and 20 min after the remifentanil infusion was terminated (T5). Arterial blood gases and pH were measured at T1, T4, T5 and maintained constant. Bladder temperature was monitored continuously. The study was completed 20 min after termination of the remifentanil infusion.

Statistical analysis
Data were analyzed using the Wilcoxon Signed Rank test. MAP, CPP, ICP, and CBFV during baseline (T1) were compared with corresponding data at T2, T3, T4, and T5. PaO₂ and PaCO₂ during baseline (T1) were compared with corresponding data at T4 and T5. Level of significance was assumed at P<0.05.

Results
Table 1 shows demographic data and medication of the 20 investigated patients. All of the patients had suffered a severe head injury. In most of the patients only one hemisphere was affected, while three patients showed injuries in both hemispheres. Six patients had an epidural hæmatoma in the primary CT-scan, while others had a subdural hæmatoma (seven patients), a subarachnoidal hæmatoma (seven patients) or intracranial bleeding (eight patients). In five patients the skull was fractured. Six of the patients had severe brain oedema with a midline shift in four of them. In 11 patients no further injuries beside the intracranial lesions were found. Propofol and sufentanil were used for background sedation and analgesia. Catecholamines were administered to maintain MAP over 80 mmHg, and in some patients a combination of catecholamines was indicated. In one patient a combination of norepinephrine and epinephrine was used and in four patients a combination of norepinephrine and dopamine was necessary.

Figure 2 shows the physiologic variables MAP, heart rate and bladder temperature during the investigation. None of the parameters was affected by administration or withdrawal of remifentanil. Figure 3 shows the effect of remifentanil on the cerebral blood flow velocity (CBFV) was assessed in the middle cerebral artery by transtemporal approach using a 2-MHz transcranial Doppler system (TCD, Multidop P, DWL, Sipplingen, Germany). In patients with unilateral injury (according to cerebral computer-tomography) CBFV was measured in the contralateral hemisphere, while in patients with global damage the less injured hemisphere was chosen for monitoring. To ensure constant angles and depth of insonation the TCD-probe was fixed using a specially designed frame during the entire study.

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Figure 2 shows the physiologic variables MAP, heart rate and bladder temperature during the investigation. None of the parameters was affected by administration or withdrawal of remifentanil. Figure 3 shows the effect of remifentanil on the cerebral
parameters ICP, CCP, and CBFV. Neither the bolus nor the continuous infusion of remifentanil affected ICP, CPP or CBFV.

Discussion

The present study shows that the administration of remifentanil did not affect MAP, ICP and cerebral haemodynamics (CBFV) in patients with severe head injury. This was independent of the ICP at the beginning of the investigation (data not shown). After termination of the remifentanil infusion no emergency hypertension or other adverse effects occurred. This was likely related to the adequate background analgesia and sedation using sufentanil and propofol. These results suggest that on-top analgesia with remifentanil can be used in head trauma patients without any intrinsic adverse effect on ICP or cerebral circulation.

Opioids are frequently used in patients with neuronal injury despite clinical reports that these compounds may increase ICP in the presence of certain constellations. For example studies in neurosurgical and neurotrauma patients have shown that fentanyl and sufentanil elevate ICP (5, 6). However, increases in ICP along with infusion of opioids were always associated with decreases in MAP, suggesting that a rise in ICP was related to autoregulatory vasodilation and increased cerebral blood volume secondary to systemic hypotension. This is supported by an investigation in patients with brain injury and sufentanil infusion, where ICP periodically increased concomitant with a decrease in MAP of >10 mmHg but was unchanged in patients with MAP-control (7). In that study CBFV (as an index of flow) in the middle cerebral artery remained constant after sufentanil administration, which further supports the autoregulatory hypothesis (7). These studies emphasize the important role of haemodynamic variables in the genesis of intracranial hypertension following an infusion of opioids.

In contrast to the autoregulatory hypothesis in neurosurgical patients a bolus of remifentanil induced a dose-dependent decrease in MAP, while ICP remained unchanged (8). In that study the cerebral vasodilator isoflurane was used as a background anaesthetic agent, which may have attenuated the autoregulatory vasodilation to the remifentanil-induced MAP decrease. In the present study patients with severe traumatic brain injury and with a background anaesthetic regimen without impact on cerebrovascular autoregulation (propofol and sufentanil), the infusion of remifentanil did not affect MAP or ICP, which is consistent with our hypothesis.

In experimental studies narcotics such as sufentanil, alfentanil, and remifentanil decreased CBF possibly by direct arterial vasoconstriction or by suppression of cerebral metabolism (4, 9). Both mechanisms may also relate to the decrease in CBFV after infusion of high-dose remifentanil (3.0 μg·kg⁻¹·min⁻¹ i.v.) in cardiovascular patients (10). These remifentanil-induced changes in cerebral haemodynamics may contribute to secondary brain damage in patients with a head injury and low CBF. The present study was performed to investigate the effect of remifentanil on CBFV in head trauma patients using moderate concentrations of remifentanil (0.25 μg·kg⁻¹·min⁻¹ i.v.). The results showed that remifentanil does not influence CBFV. Possibly, the remifentanil-concentration in the brain was too low to induce direct cerebral vasoconstriction or cerebral metabolism was already suppressed by the background anaesthesia inhibiting a further metabolism-dependent decrease in CBF. Therefore, remifentanil infusion in a concentration comparable to the present study can be recommended as on-top analgesia without a negative influence on cerebral haemodynamics.

In the present study background anaesthesia with propofol and sufentanil was used for adequate sedation and analgesia. Remifentanil was applied on top of this sedation with potential interaction between drugs, limiting the definition of the direct effects of remifentanil on MAP, ICP and CBF in head trauma patients. However, the intention of the present study was to investigate MAP, ICP and CBF effects of remifentanil when used on top of a pre-existing sedative and analgetic regimen, and therefore the combination

![Fig. 3. Intracranial pressure (ICP, [mmHg]), cerebral perfusion pressure (CPP, [mmHg]), and cerebral blood flow velocity (CBFV, [cm·s⁻¹]) during baseline (T1), after 1 min (T2), 5 min (T3) and 20 min (T4) of remifentanil administration, and 20 min after termination of remifentanil administration (T5). Data are represented as mean with a confidence interval of 95%.

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of the drugs appears to be appropriate and realistic in terms of the given clinical constellation. The use of vasopressors to maintain MAP above 80 mmHg may represent a confounding factor during the present investigation, as catecholamines may affect cerebrovascular tone and in turn CBFV. However, when norepinephrine (0.2–20 μg·min⁻¹) and epinephrine (2–10 μg·min⁻¹) were administered into the carotid artery in neurosurgical patients, there was no effect on the regional CBF or on the hemispheric mean flow values (11). The concentrations of catecholamines were comparable to those used in the present study, and therefore it is unlikely that vasopressors affected CBF in our patients.

In conclusion, the present study suggests that administration and withdrawal of remifentanil does not affect MAP, ICP, and CBFV in head-injured patients at the intensive care unit. Since remifentanil possesses a very short plasma half-life it is most suitable for on-top analgesia during painful stimuli in combination with a background anaesthesia with, for example, sufentanil and propofol in ventilated patients on the intensive care unit.

References