Supplementation of general anaesthesia with tramadol or fentanyl in parturients undergoing elective Caesarean section

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Purpose: Tramadol has been recommended for analgesia in parturients undergoing vaginal delivery. The present report investigated the effect of tramadol *versus* fentanyl on umbilical vein (UV) blood gases and Apgar scores of neonates delivered via elective Caesarean section under general anaesthesia.

Methods: Forty ASA I or II parturients undergoing elective Caesarean section were included in a randomized double-blinded study . The patients were divided into a tramadol (n = 20) and fentanyl groups (n =.20) . During preoxygenation, one group received 100 mg tramadol *iv*, while the second received 100 μg fentanyl. Anaesthesia was induced in both groups by 3 mg·kg^{-1} thiopentone and 1.5 mg·kg^{-1} succinylcholine was given to facilitate tracheal intubation. Anaesthesia was maintained during the induction-delivery period with nitrous oxide 50% in oxygen.

Results: The umbilical vein PO_2 was higher in the fentanyl (34 ± 5 mmHg) than in the tramadol group (24 ± 6 mmHg) ($P < 0.01$), while the UV PCO_2 was higher in the tramadol group (50 ± 5 *vs* 45 ± 4 mmHg) ($P < 0.01$). The Apgar scores at one and five minutes were not different between the two groups. Post operatively, two patients in the tramadol group recalled the crying of their newborn at delivery.

Conclusion: Tramadol is associated with a high incidence of intraoperative maternal recall and can result in lower umbilical vein PO_2 and higher PCO_2 than in the fentanyl group.

Objectif : Le tramadol a été recommandé pour l'analgésie des parturientes lors d'un accouchement par voie vaginale. La présente étude a exploré l'effet du tramadol *versus* celui du fentanyl sur les gaz veineux ombilicaux et sur les indices d'Apgar des nouveau-nés lors d'une césarienne sous anesthésie générale.

Méthodes : Quarante parturientes ASA I ou II subissant une césarienne élective ont participé à l'étude randomisée en double aveugle. Les patientes ont été réparties en deux groupes, celui du tramadol (n = 20) et celui du fentanyl (n = 20). Pendant la préoxygénation, un groupe a reçu 100 mg de tramadol IV, pendant que le second a reçu 100 μg de fentanyl. L'anesthésie a été induite dans les deux groupes par 3 mg·kg^{-1} de thiopental et 1,5 mg·kg^{-1} de succinylcholine a été administré pour faciliter l'intubation endotrachéale. L'anesthésie a été maintenue pendant la période induction-accouchement avec 50 % de protoxyde d'azote et d'oxygène.

Résultats : La PO_2 de la veine ombilicale était plus élevée avec le fentanyl (34 ± 5 mmHg) qu'avec le tramadol (24 ± 6 mmHg) ($P < 0.01$), tandis que la PCO_2 de la veine ombilicale était plus élevée avec le tramadol (50 ± 5 *vs* 45 ± 4 mmHg) ($P < 0.01$). Les indices d'Apgar à une et cinq minutes n'étaient pas différents dans les deux groupes. À la suite de l'intervention, deux patientes du groupe tramadol ont déclaré avoir entendu le cri de leur bébé à la naissance.

Conclusion : L'usage du tramadol, comparé à celui du fentanyl, est associé à une plus grande incidence de conservation de la conscience des mères pendant l'accouchement et peut avoir comme résultat une PO_2 de la veine ombilicale plus faible de même qu'une PCO_2 plus élevée.

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GENERAL anaesthesia for Caesarean section is a challenge to the anaesthetist who has to satisfy the conflicting requirements of the mother *versus* her infant.[1] The anaesthetic technique must prevent maternal awareness, while the infant must be adequately oxygenated, and be spared the effects of depressant drugs crossing the placenta.[2] Eisele *et al.* administered 1 $\mu g \cdot kg^{-1}$ fentanyl *iv* prior to Caesarean-delivery, and found no adverse effects on Apgar scores, or on umbilical cord blood gases of the neonates.[3]

Tramadol is a new centrally acting analgesic drug. It has been found both *in vivo* and *in vitro* to have a low but preferential activity at μ opioid receptors, and also to inhibit both noradrenaline and 5-hydroxy-tryptamine (5-HT) neuronal reuptake and to facilitate 5-HT release.[4–8] Analgesia produced by tramadol is mediated via both stimulation of μ-opioid receptors and modulation of central monoaminergic inhibitory pain pathways. Tramadol, in contrast to other opioid analgesics, has not been associated with clinically respiratory depression[4–8] and, hence, it has been recommended for obstetric analgesia during vaginal delivery;[9] 100 mg tramadol is equianalgesic to 100 mg meperidine, with a lower incidence of neonatal respiratory depression.[10] The adequate analgesic effects of tramadol, associated with the absence of respiratory depression of neonates suggest that tramadol may be also suitable to supplement general anaesthesia in parturients undergoing Caesarean section.

The present report used tramadol for supplementation of nitrous oxide:oxygen anaesthesia in a group of patients undergoing elective Caesarean section, and compared the umbilical vein blood gases and the Apgar scores of the newborns with that achieved in parturients in whom fentanyl was used to supplement anaesthesia.

Methods

The investigation was carried on 40 parturients undergoing elective Caesarean section under general anaesthesia. The research was approved by the Institution Research Committe, and informed consent was obtained from all patients. All parturients were ASA classification I or II; gestational age of at least 36 wk, with no active medical or obstetric complications.

Premedication consisted of 0.5 mg atropine *im*. In the operating room, a large bore *iv* catheter was inserted, and patients were given 1500-2000 ml lactated Ringer's solution throughout the surgical procedure. Pulse oximeter, ECG, non-invasive arterial blood pressure and end-tidal carbon dioxide tension were continuously monitored. All patients were in the supine position, while left uterine displacement was applied. Patients were preoxygenated with oxygen 100%, five minutes before induction of anaesthesia, and were randomly allocated into two groups. Each group consisted of 20 patients: tramadol group (T), and fentanyl group (F). During preoxygenation, 100 mg tramadol *iv* were injected in the T group, while 100 μg fentanyl were given in the F group to be followed, in both groups, by rapid-sequence induction of anaesthesia with 3 $mg \cdot kg^{-1}$ thiopentone and 1.5 $mg \cdot kg^{-1}$ succinylcholine to facilitate tracheal intubation. In the two groups, the trachea was intubated with a cuffed endotracheal tube while applying cricoid pressure. During the induction-delivery period, anaesthesia was maintained in both the F and T groups with N_2O 50% in 0_2. Intermittent positive pressure ventilation was carried out in all patients. After recovery from succinylcholine, muscle relaxation was maintained with 0.1 $mg \cdot kg^{-1}$ vecuronium. Following delivery, anaesthesia was maintained in the two groups with $N_2O : 0_2$ mixture (2:1). Additional analgesia was provided with further administration of 50 mg tramadol in the (T) group, and 50 μg fentanyl in the (F) group. At the end of surgery, neuromuscular block was reversed with a mixture of 0.02 $mg \cdot kg^{-1}$ atropine and 0.05 $mg \cdot kg^{-1}$ neostigmine. Following recovery from anaesthesia, the parturients were interviewed concerning any recall during surgery, and were observed for postoperative nasuea and/or vomiting.

A record was made of the time from induction of anaesthesia until delivery of the newborns (I-D time), as well as the uterine incision-delivery time. Also, the maternal end-tidal $PC0_2$ and the oxygen saturation at the time of delivery were recorded. Following delivery, all newborns were examined by a paediatrician who was blinded to the anaesthesia technique. Apgar scores were recorded at one and five minutes. Also, umbilical vein (UV) blood samples were obtained at delivery from a double-clamped segment of umbilical cord and the UV blood gases were analyzed. After 24 hr, the neurobehavrioural responses of the neonates were evaluated by a paediatric resident who was blinded to the anaesthesia technique.

Chi-square analysis was used to compare the Apgar scores, as well as the incidence of recall or vomiting. Other data are reported as mean ± standard deviation. Student's t test was used to compare data between the two groups. $P < 0.05$ was considered significant.

Results

Demographic data

There were no differences between the two groups, with regard to the age of parturients, their body weight and gestational age. Also, the induction-delivery time,

as well as the end-tidal PCO_2 and oxygen saturation at the time of delivery were not different (Table I).

Umbilical vein blood gases

The UV $P0_2$ was lower and the UV PCO_2 was higher in the tramadol group than in the fentanyl group. The UV base deficit (BD) values in the two groups were not different (Table II).

Apgar scores and neurobehavioural responses

The Apgar scores, ≥ 7 at one and five minutes, were not different between the two groups. After 24 hr, neurobehavioural assessment did not show any difference between the two groups (Table III).

No patient in the fentanyl group had any intraoperative recall, while two patients in the tramadol group recalled crying of their newborns at the delivery time; no pain was experienced at that time. Also, no patients in the fentanyl group complained of nausea and/or vomiting, while four patients in the tramadol group experienced postoperative nausea and vomiting.

Discussion

It has shown in parturients undergoing elective Caesarean section under nitrous oxide:oxygen anaesthesia, that the umbilical vein $P0_2$ of the newborn is proportional to the maternal $Pa0_2$; increasing the $Fi0_2$ from 0.2 to 0.5 is associated with an increase of umbilical vein $P0_2$.[11] In the present report, the same $Fi0_2$ of 0.5 was used in the two groups of patients; however, the umbilical vein $P0_2$ and PCO_2 differed according to the drug used to supplement nitrous oxide:oxygen during the I-D period. In the tramadol group, the umbilical vein $P0_2$ was lower and the umbilical vein PCO_2 was higher than the corresponding values in the fentanyl group.

Uterine blood flow (UBF) is an important determinant of foetal oxygenation. The UBF at term is approximately 10% of the cardiac output. The uterine vascular bed is thought to be almost maximally dilated under normal conditions, with little capacity to dilate further.[12] However, it is capable of marked vasoconstriction by α-adrenergic action. Vasopressors with predominant α-adrenergic activity, such as methoxamine, phenylephrine, angiotensin or norepinephrine have been shown to diminish UBF and lead to foetal asphyxia.[13,14] Tramadol blocks the reuptake of NE and 5-HT at the nerve terminal.[4–8] Norepinephrine can result in uterine vasoconstriction. Also, 5-HT can produce vasoconstriction, and amplifies the local constrictive action of norepinephrine.[15] Thus, it is postulated that tramadol may induce vasoconstriction of the uterine blood vessels with a consequent decrease of umbilical vein $P0_2$ and an increase of umbilical vein PCO_2.

The 5-HT action of tramadol may explain the higher incidence of nausea and vomiting in the tramadol group: 5-HT acting at $5\text{-}HT_3$ receptors, is an important emetic signal and transmitter in the chemoreceptor trigger zone and in the solitary tract nucleus.[16] Also, a major drawback to the use of tramadol in anaesthesia is the risk of intraoperative awareness,[7] which may be attributed to the low opioid receptor agonist action of tramadol, and its preferential action on the monoaminergic pathways.

In contrast with tramadol, fentanyl is a selective opioid receptor agonist, with no effect on norepinephrine neuronal reuptake, or 5-HT release. In the fentanyl group, no maternal awareness was reported. Also, the UV $P0_2$ values were higher and the UV PCO_2 values were lower than the corresponding values in the tramadol group. Fentanyl rapidly crosses the

TABLE I Age, body weight, Induction-delivery (I-D) time, and uterine incision-delivery time (UI-D) in the two groups of parturients, as well as the percentage oxygen saturation ($SP0_2$), and the end-tidal $PC0_2$ ($ETC0_2$) at the time of delivery. No significant difference between the two groups.

	Demographic data					
	Age (yr)	*Body Weight (kg)*	*I-D Time (min)*	*UI-D Time (sec)*	*$Sp0_2$%*	*$P_{ET}C0_2$(mmHg)*
Fentanyl Group	30 ± 5	75 ± 7	11 ± 4	92 ± 7	99.3 ± 0.7	30.3 ± 3.9
Tramadol Group	30 ± 5	75 ± 12	9 ± 2	90 ± 5	98.8 ± 1.3	30.5 ± 3.6

TABLE II Umbilical vein $P0_2$, $PC0_2$, pH, $HC0_3^-$ and base deficit (BD) in the two groups of parturients

	Umbilical vein blood gases				
	PO_2 (mmHg)	*$PC0_2$ (mmHg)*	*pH*	*$HC0_3$*	*BD*
Fentanyl Group	34 ± 5	45 ± 4	7.34 ± 0.02	24.5 ± 1.8	-1.2 ± 1.8
Tramadol Group	24 ± 6	50 ± 5	7.31 ± 0.03	25 ± 1.4	-0.72 ± 1.3
P	< 0.01	< 0.01	< 0.01	> 0.05	> 0.05

TABLE III Apgar scores of the newborns at one and at five minutes. No significant difference between the two groups.

	Apgar score	
	1 minute ≥ 7	*5 mintues ≥ 7*
Fentanyl Group	17/20	20/20
Tramadol Group	18/20	20/20

placenta to the foetus,[17] but has no adverse effects on uterine tone or blood flow. Despite the finding of lower UV $P0_2$ and higher $PC0_2$ values in the tramadol group than in the fentanyl group, the conditions of the neonates as evidenced by the Apgar scores were not different. Also, the UV base deficit and the neurobehavioural assessments were not different between the two groups.. However, these results may only apply to elective Caesarean section with no foetal distress. Animal experiments suggest that in the normal placenta there is "safety factor" of approximately 50% in the UBF i.e. the UBF will decrease to half its normal value before severe foetal acidosis becomes evident and oxygen uptake declines.[18]

In conclusion, the present report shows that in parturients undergoing elective Caesarean section, supplementation of $N_20:0_2$ by tramadol during the I-D period is associated with a high incidence of maternal intraoperative recall, and can result in lower UV $P0_2$ and higher UV $PC0_2$ than the corresponding values achieved in the fentanyl group.

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