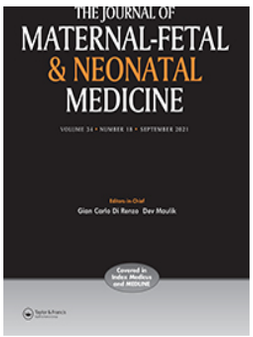

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SHORT REPORT

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Nalbuphine: a candidate for treatment of women overwhelmed with sudden, intense labor pain?

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ABSTRACT

Aim: On very rare occasions, women are overwhelmed with sudden, intense labor pain in the context of ultra-rapid late second stage of labor, especially when the head is crowning. The consequences may comprise serious pelvic floor damage for the mother and hypoxia for the fetus. Drugs like nalbuphine for immediate maternal analgesia and sedation would be helpful. This mixed opioid agonist–antagonist, that was used in obstetric anesthesia in the 1980s, acts quickly while side effects for the mother are minor. To better estimate possible complications for the fetus of a use shortly before birth, it is important to find out how quickly i.v. administered nalbuphine reaches fetal circulation. Therefore, we characterized the transplacental transfer of nalbuphine using an *ex vivo* model.

Methods: Placentas were obtained from cesarean sections after mothers gave their informed consent. Upon cannulation of one cotyledon, nalbuphine was added to the maternal circuit (calculated final concentration 100 ng/mL) and the *ex vivo* placenta perfusions were performed. To determine nalbuphine transfer from maternal to fetal circuit in the successful perfusions ($n = 5$), samples were collected at different time points.

Results: At perfusion start, the measured initial nalbuphine concentrations in the maternal and fetal circuits are 93.1 and <0.1 ng/mL, respectively. After 5 min of placenta perfusion, 2.5 ng/mL nalbuphine (i.e. 3% of the initial nalbuphine concentration in the maternal circuit) is reached in the fetal circuit; after 15 and 30 min, 9.7 and 15.8 ng/mL (approximately 10 and 16% of initial maternal, respectively).

Conclusions: Only a small amount of nalbuphine is likely to reach the fetus during the first minutes after (i.v.) maternal administration. Nalbuphine might be a valuable candidate for clinical use in the i.v. analgesia and sedation of women overwhelmed with sudden labor pain in the context of ultra-rapid second stage of labor.

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Nalbuphine; placental barrier; ultra-rapid labor; placenta perfusion; analgesia

Introduction

On very rare occasions, women are overwhelmed with sudden, intense labor pain, where it would be helpful to have drugs for immediate maternal analgesia and sedation. Especially in the context of ultra-rapid late first and second stages of labor, they flail and reject any help from health professionals. In such situations, application of an epidural or spinal anesthesia could lead to serious injuries and it is too late for general anesthesia. The consequences are fetal hypoxia in cases of prolonged pushing and serious pelvic floor damage for the mother, which can lead to psychological and somatic morbidity and thus to a reduced quality of life. Symptoms such as post-traumatic stress disorder are common.

With its clinical spectrum of effectiveness – and especially with its high safety profile – the opioid nalbuphine could be a persuasive means of overcoming these problems. Its analgesic efficacy is comparable to morphine [1], but nalbuphine has ceiling effects as analgesic and on ventilatory depression; side effects are rare [2]. The exceptional safety profile is due to nalbuphine being not only agonistic on the κ-opioid

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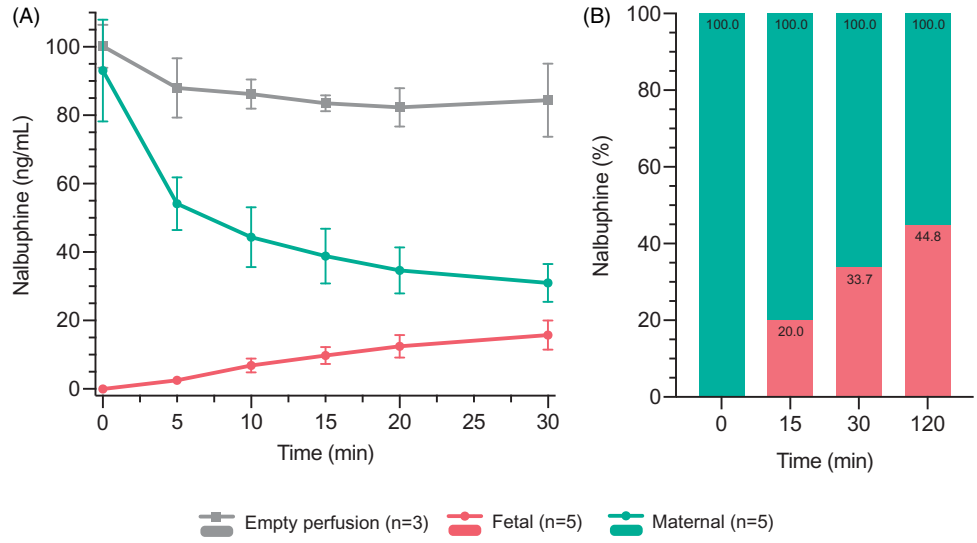

Figure 1. Perfusion profiles of nalbuphine. (A) Data from independent placenta perfusions (fetal and maternal circuits, $n = 5$) and empty perfusions (maternal circuit only, $n = 3$); displayed are the mean concentrations ± SD. (B) Nalbuphine relative concentrations data in the fetal and maternal circuits at 15, 30, and 120 min.

receptor, like all other opioids, but also mainly antagonistic on the μ-opioid receptor [3]. For these reasons, nalbuphine has a wide therapeutic range, being used to treat low to moderately painful conditions, in particular when an accompanying sedative effect is favorable. In situations in which a good anesthesia safety profile is particularly crucial, such as in neonates, infants, or small children, nalbuphine is often the opioid of choice [2,4,5].

Nalbuphine was introduced as a systemic obstetric analgesic in the 1980s, and its safety profile presented also as such an advantage over other opioids that are also known to cross the placental barrier [3,6]. In modern obstetric anesthesia, nalbuphine plays only a neglectable role. Nalbuphine's benefits could, however, be helpful to women steamrolled with sudden, intense labor pain. To better estimate the chances of side-effects in neonates after i.v. application in the last minutes before delivery, we have now characterized the immediate transplacental transfer of nalbuphine using the *ex vivo* placenta perfusion model (see Methods under Supplementary material).

Results

At perfusion start, the measured nalbuphine concentrations in the maternal and fetal circuits are 93.1 and <0.1 ng/mL, respectively. Figure 1(A) shows that after 5 min of placenta perfusion, 2.5 ng/mL (approximately 3% of the nalbuphine initially added to the maternal circuit) is detected in the fetal circuit; after 15 min, 9.7 mg/mL (10%); and after 30 min, 15.7 mg/mL (17%). At the same time, empty perfusions' results reveal only minor decreases of down to 84% of the initial nalbuphine concentration (Figure 1(A)).

Focusing on the relative nalbuphine concentrations measured in maternal and fetal circuits only (Figure 1(B)), the results show that after 15 min the concentration in the fetal circuit is four times lower that in the maternal circuit, after 30 min the concentration in the fetal circuit is still lower than the one measured in the maternal circuit. As to be expected, 120 min after beginning perfusion, nalbuphine concentrations in the two circuits are comparable indicating that equilibrium between the two circuits has been reached. The latter data show moreover that the two circuits were connected under our experimental conditions, corroborating the validity of our results.

Discussion

Our results obtained show that the transfer of nalbuphine through a cotyledon in the placenta perfusion model is not immediate: it takes several minutes to transfer a small part of the nalbuphine present in the maternal circuit to the fetal circuit, even after half an hour no equilibrium between the two compartments has been achieved.

One of the strengths of the present study is that the measured initial concentration of 93.1 ng/mL nalbuphine in the maternal circuit is even higher than the maximal maternal plasma concentration determined in a previous study [6]. Another strength is the use of human placenta perfusion that is the gold-standard for studying transplacental transfer at term, i.e. at exactly the time point of interest for delivery-

related research questions. Limitations of our work derive from differences between the placenta perfusion model and the *in vivo* situation. These comprise, in addition to different times needed for drug arrival at the critical transfer place (mounted cotyledon in the perfusion model and placental barrier *in vivo*), distinct compartments' volume.

Taken together, our results suggest that nalbuphine might be a valuable candidate for clinical use in the i.v. analgesia and sedation of women overwhelmed with sudden, intense labor pain in the context of ultra-rapid late second stage of labor, when application of an epidural or spinal anesthesia could lead to serious injuries and it is too late for general anesthesia.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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