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Remifentanil for labour pain relief

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Abstract

Labour is thought to be one of the most intense and painful experiences in a woman's life. Numerous studies using a Visual Analogue Scale invariably demonstrate that 20% of women in labour describe the pain as "unbearable" and 60% describe the pain as "very intense". Since the mid-1980s, continuous epidural analgesia during labour has been considered the gold standard of labour anaesthesia and is currently the most frequently used. There are situations in which this type of analgesia could not be used. An alternative pain management is administration of parenteral opioids, the most frequently used of which is pethidine. Its use is associated with adverse effects and unsatisfactory analgesia. Since the second half of the 20th century, a new generation of opioids, such as fentanyl or remifentanil, has been used. Despite their much better pharmacokinetic and pharmacodynamic parameters, obstetricians, midwives and neonatologists are most aware of pethidine, probably because it has been used for the longest period of time, despite its disadvantages and the risk that its use entails. The drug that is nearest to ideal is remifentanil. The countries in which it is widely used as an alternative type of labour anaesthesia have developed practice standards or guidelines practice. Guidelines and alternatives to pethidine protocols for effective labour analgesia in Poland might be merited.

Key words: labour, pain, analgesia; opioids, remifentanil

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Spontaneous vaginal delivery is considered to be one of the most painful experiences in a woman's life [1]. The intensity of pain depends on many factors, some of which have been determined, including the individual pain tolerance, foetal position and weight, strength of contractions, myometrial tone and earlier labour-related experiences [2].

Age, ethnicity, cultural factors, education, socioeconomic status, pre-partum education of expectant mothers, parity and psychological attitudes of parturients are of importance as well [3]. The relationship between the severity of labour pain and a history of dysmenorrhoea has been observed. The probable cause of this phenomenon is the excessive production of prostaglandins. Primiparas reported lower labour pain intensity than multiparas, which is likely to result from the extensive knowledge of delivery provided by the mass media [4].

Compared to other types of pain, labour pain is assessed by primiparas and multiparas as a pain of slightly lower intensity than that accompanying causalgia or finger amputation yet substantially exceeding phantom pain; persistent and recurrent pain in neuralgia or postherpetic neuralgia; and pain in neoplastic diseases, excluding the terminal stages. Numerous studies demonstrate that 20% of parturients describe the pain as "unbearable" and 60% as "very intense" according to the visual analogue scale (VAS). With due respect for the concept of natural childbirth, it appears that effective labour analgesia should be considered in mothers experiencing pain most strongly [5].

Severe pain adversely affects parturients and foetuses. Pain-induced stress accelerates the basal metabolism of a parturient and increases cardiac output and ventilation. In extreme cases, reflex hyperventilation leads to respiratory

alkalosis manifesting with maternal tetany and foetal cardiac arrhythmia. Maternal respiratory tetany shifts the haemoglobin dissociation curve to the left, leading to deterioration of the transplacental oxygen transport. The sympathetic stimulation and increased endogenous catecholamine concentration cause uterine vasoconstriction, which reduces the utero-placental flow and is likely to lead to intrauterine foetal hypoxia and acidosis. Additionally, lipolysis, the release of free fatty acids freely permeating the placenta, and hyperglycaemia are observed, which increases foetal hypoxia and acidosis [6]. Released catecholamines impair uterine contractile function, which prolongs the delivery and secondarily deteriorates the postpartum status of the newborn [7].

Labour pain that is experienced strongly could adversely affect the later attitude of the mother to her child, and in many cases, psychological support or psychiatric treatment is required [8]. Many women consider delivery to be unpleasant, unnecessary, and undesirable as well as emotionally and physically ravaging [9]. Negative emotions during delivery negatively influence the lives of women and their children by altering many important spheres of life, e.g., the emotional and intimate life of women, family bonds, or the sense of security in children [10]. These undesirable factors could be divided into four categories associated with the following situations:

— the acceptance of medical interventions, such as labour induction, instrumental labour, emergency Caesarean section, and transfer of newborns to the intensive care unit;
— the previous life of women, the desire for having children, and satisfaction with relationships with men;
— the general physical and mental state of women during delivery, i.e., the experienced pain and its control;
— the personnel comportment in the delivery room [11].

Since the mid-1980s, continuous epidural anaesthesia (CEA) for labour and delivery, which is de facto continuous analgesia, has been considered the "gold standard". This type of analgesia is used most commonly, although it could not be offered to each parturient. CEA for labour should not be used in cases with medical, technical (excessive obesity of the parturient) or organisational (an anaesthesia team is unavailable throughout the procedure) contraindications. In such cases, an alternative method of pain relief should be widely available, globally as well as in Poland. Recommendations for analgesic management in gynaecology and obstetrics were published in 2008 [12]. The use of opioid drugs is recommended in the second section of the guidelines pertaining to pain treatment in pregnant women, parturients and women in the puerperium period.

Opioids have been used in obstetrics for over 100 years for their analgesic properties, although the first report of their use in parturients to alleviate labour pain appears in Chinese writings. Since 1902, a mixture of morphine and scopolamine has been administered; however because of the adverse side effects, i.e., confusion, excitation, maternal memory disorders or foetal respiratory depression, its usage was abandoned after several years. Another opioid drug – pethidine – was produced in 1939, and it has been used in obstetrics since 1950 and is the most common opioid administered during delivery. In many hospitals, particularly in those with low numbers of deliveries, this drug is the analgesic of choice [13]. In the United States, the incidence of parenteral administration of opioids ranges from 30% in hospitals with more than 1500 deliveries annually to 56% in hospitals with 500-1500 annual births. In small hospitals, i.e., those with fewer than 500 deliveries per year, parenteral opioids are used in 50% of the deliveries. In Great Britain, this percentage is approximately 38%, on average [14].

In the second half of the 20th century, newer opioid drugs, such as fentanyl, alfentanyl, and remifentanil, were introduced. Despite their markedly better pharmacokinetic and pharmacodynamic properties, pethidine has been favoured by obstetricians, midwives and neonatologists, which has most likely resulted its long-term use, in spite of its disadvantages and the resultant risks of adverse effects. When administered intramuscularly, its action is uncontrollable in mothers and infants and the highest concentration in foetal blood is observed 2–3 hours after injection.

In spontaneous vaginal deliveries, the moment of birth is difficult to anticipate; it is likely that the child will be born when pethidine has reached its peak concentration in the maternal circulation, which creates a danger of respiratory depression in the newborn. A similar effect is exerted by the active metabolite of pethidine — norpethidine. In many cases, it leads to re-development of a narcotic effect in the infant, which is relevant because the half-life of pethidine is 15–23 hours in newborns and 2–3 hours in mothers. This occurrence results from the slower elimination of norpethidine from foetal circulation because of slowed down placental flow and the lower competence of the liver. According to the literature reports, the half-life of pethidine and norpethidine could reach 20–60 hours [15].

Neonatologists have observed that the children of mothers administered pethidine are less viable and could have respiratory problems as well as lower Apgar scores and Neurologic and Adaptive Capacity Scores (NACSs) [16]. Mothers could develop nausea, vomiting, somnolence, balance disorders and respiratory depression [17, 18]. Self-assessed good-to-excellent pain relief in the first and second period of delivery was reported by only 50% of the women administered intramuscular pethidine. For comparison, this percentage was 88% in the group of parturients administered CEA for labour [19].

The unfavourable profile of the earlier generation of opioids was an incentive to develop a safe analgesic for controlled supply in fractionated doses and to ensure maximum safety and satisfactory analgesia. Ultra-short acting remifentanil (RMFNT) fulfilled these conditions. This drug shows a strong affinity to mu-opioid receptors MOR (μ), and a weaker affinity to DOR (δ) and KOR (κ). It is characterised by a quicker onset of action, low distribution volume and rapid redistribution, which in clinical practice translates to simple titration [20]. After intravenous administration, the analgesic effect is nearly immediate, and it subsides several minutes after the completion of the infusion; the residual opioid activity persists for less than 10 minutes. Remifentanil does not trigger the release of histamine and does not induce late inhibition of respiratory functioning. It binds with plasma proteins at a rate of 70%. It is metabolised by non-specific blood and tissue esterases to nearly analgesically inactive carboxyl acid, which is characterised by activity 46,000 times lower than that of the original drug; hence, it induces no analgesic effects. The $T_{0.5}$ of RMFNT is approximately 3 minutes; the $T_{0.5}$ of its metabolite is approximately 2 hours. Approximately 95% of remifentanil is excreted in urine in the form of its metabolite [21]. RMFNT crosses the placenta barrier, and its concentration in foetal blood is approximately 50% of the concentration in maternal blood; the drug is likely to be metabolised in the foetus, thus it could have inhibiting effects on the respiratory centre of newborns. The effects on the foetus of remifentanil administered in fractionated doses are markedly less than the effects of pethidine administered routinely in a bolus dose without control [22].

In Europe and the United States, RMFNT has been used in clinical practice since 1995 [23]. In 1998, the first report describing its use in obstetrics was published. The drug was used to supplement epidural analgesia for scheduled Caesarean sections [24].

In further publications, the benefits resulting from the use remifentanil were emphasised in a group of women with contraindications for CEA during delivery. Those encouraging reports were followed by a study by Olufolabi published in 2000 [25], which provoked a vibrant discussion confirmed by clinical trials regarding the use of remifentanil in obstetrics. Olufolabi questioned the efficacy of delivery analgesia with remifentanil because, according to his findings, its analgesic effect lasted only 60 minutes during infusion, and subsequently, the pain recurred with the same or higher intensity and increased doses had no analgesic effects. The authors of papers published in 2001–2002 were more balanced in their opinions; nevertheless, all of the authors agreed that remifentanil was not an alternative to CEA for labour, although it could be useful for parturients for whom an epidural block was contraindicated and as an alternative to intramuscular pethidine.

None of these publications described the lack of an analgesic effect within 60 minutes after the onset of infusion; these studies emphasised the possible use of remifentanil, particularly in cases with contraindications for an epidural block [26–29]. The risk of respiratory depression should not be ignored, and patients receiving RMFNT should be appropriately monitored [28].

In the following years, the use of pethidine for labour pain relief was increasingly criticised. First, its sedative effects were stressed, followed by its analgesic action. Remifentanil exerted a sedative effects as well; however, because of its short action, the sedative effects were not as dangerous as were those of pethidine, and newborns after delivery with RMFNT analgesia had better scores, according to different scales, than the newborns administered pethidine [30].

In a randomised, double blind study comparing analgesic effects of remifentanil and pethidine during delivery, both drugs were administered intravenously by a patient-controlled analgesia system (PCA) [31]. The study was discontinued because of the markedly lower Apgar scores of newborns in the pethidine group. The authors concluded that remifentanil induced good delivery of analgesia.

In the countries in which remifentanil is widely used during deliveries as an alternative to block analgesia, standards or guidelines of management have been developed [32, 33]. In Great Britain, remifentanil has been used in 1/3 of the hospitals for over 12 years [34, 35]. In Northern Ireland, it was introduced into obstetric practice in 2004 and is used in over 1200 patients annually. In the 2000s, a 20-year study comparing the efficacy and safety of remifentanil analgesia (in 1508 parturients), continuous epidural analgesia (1200 parturients) and intramuscular pethidine (1789 parturients) for delivery was conducted. Resuscitation was needed most commonly in the newborns of mothers undergoing epidural blocks, as opposed to those receiving remifentanil. The conclusion of the study was that remifentanil should be available for analgesia [36].

Remifentanil is used in 1/3 of all of the obstetric hospitals in Holland [37], in which guidelines of management and delivery analgesia protocols have been devised [38]. In Italy, a study was conducted with a group of 205 parturients receiving RMFNT, and no newborn required naloxone [39]. In Finland, the effect of meperidine, fentanyl and remifentanil was compared in the children of 159 parturients. The analysis of the 1- and 5-minute Apgar scores and NACSs demonstrated substantially weaker effects of remifentanil on the postpartum condition of the newborns, compared to those of the other opioids [40]. A Canadian study comparing the postpartum conditions of newborns of mothers receiving remifentanil (47) or fentanyl (51) confirmed a higher safety profile for remifentanil, based on the lower percentage of newborns requiring resuscitation [41]. The authors

of a study comparing intravenous remifentanil by PCA and intramuscular pethidine in a population of 69 women in Hong Kong demonstrated similar postpartum conditions of the newborns in both groups; markedly better pain relief was observed in the remifentanil group [42].

In Norway, it is estimated that pethidine is used in approximately 77% of deliveries. The drug is firmly established in the practices of midwives, who unwaveringly order it. Nevertheless, even in this country, small changes have been observed [43].

In the Department of Obstetrics and Pathology of Pregnancy of the Pomeranian Medical University from 2003–20004, remifentanil analgesia by PCA was administered for delivery. The levels of maternal satisfaction and pain relief during the deliveries and the postpartum conditions of the newborns were assessed and presented in a paper published in Anaesthesiology Intensive Therapy [44]. The conclusions were consistent with the findings of other authors. It was demonstrated that the satisfaction with the method of analgesia used was comparable in the group with continuous epidural analgesia by PCA and in the group receiving intravenous infusions of remifentanil (by PCA); remifentanil analgesia was found to be a safe alternative to a continuous epidural block, particularly in women with a contraindication for epidural analgesia.

Based on the Apgar scores and parameters of the acid-base balance, the team of neonatologists did not recommend that analgesia with (RMFNT) is superior to the methods used to date [45, 46]. However, small samples were examined (23 newborns in the remifentanil group and 31 in the epidural analgesia group), which deserves attention. Iranian researchers compared the results of newborns of mothers who were administered remifentanil and those of mothers who received pethidine. Their conclusion was that newborns should be assessed by neonatologists blind to the information of which opioid was used for analgesia [47].

In 2012, a meta-analysis of 12 randomised controlled studies was published; remifentanil, pethidine, nitrous oxide, an epidural block, and fentanyl were used in these studies. The meta-analysis focused on 2001–2011. Remifentanil was found to have higher efficacy and safety than pethidine. Additionally, the basic safety principles of opioid use and the need for SpO2 continuous monitoring as well as observation of the patients to detect possible respiratory depression were highlighted [48].

The number of anaesthesia procedures in which remifentanil is used is substantially higher than is shown by the data from many centres, including Polish centres, Studies and published results in scientific journals have not been required, and the actual extent of the phenomenon is unknown.

There are no Polish standards for analgesia in spontaneous vaginal deliveries other than regional blockade, which is not always available; guidelines and recommendations for an analgesia alternative to pethidine and CEA are essential and should be devised.

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