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EDITORIAL

A broadening choice for labor analgesia: remifentanil on the à la carte menu

How wonderful to be Queen Victoria as she chose an à la carte labor analgesia option from her physician, Dr. John Snow. Chloroform was not routinely available for labor analgesia in 1853, yet Queen Victoria was able to enjoy comfortable labor using it. A vision for the future could be a laboring woman ordering her desired labor analgesia from the à la carte menu options on her mobile device according to the strength of analgesia desired and the risk/benefit profile she preferred.

Epidural analgesia represents gold standard analgesia for laboring women.[1] However, alternatives should be available for women who decline epidural analgesia or those unable to receive it due to medical contraindications. The chief alternative pharmacologic agents available include inhaled nitrous oxide; intramuscular (IM) or intravenous (IV) pethidine (meperidine), morphine or diamorphine; or IV patient-controlled analgesia (PCA) with fentanyl or remifentanil.[2,3] In terms of analgesic efficacy and overall satisfaction, remifentanil is probably the best alternative to labor epidural analgesia.[4–6]

In this volume of IJOA, three European studies present aspects of safety and maternal satisfaction with remifentanil for labor analgesia.[7–9] The RemiPCA Network voluntary reporting system, initiated by Melber et al. in Switzerland,[7] summarized data between 2010 and 2015 from 31 centers that worked according to a standard operating procedure (SOP). The SOP has been intermittently amended since development in response to data received via the Network, and to reports of serious adverse events (SAE) in the current literature.[5,10,11] Murray et al. provided a unique single-center description of their experience in Northern Ireland using remifentanil PCA for labor from its embryonic stage.[9]

Logtenberg et al.[8] reported SAEs in the Netherlands associated with remifentanil PCA during labor, with 61 hospitals participating in the review. They too described the use of an SOP, however, in contrast to the other two publications that recommend continuous one-to-one midwifery care, the Dutch SOP does not mandate one-to-one care beyond the first hour of administration. Logtenberg et al. reported 27 cases of SAEs, which included one case of cardiac arrest (due to a PCA pump error) that may have been avoided with one-to-one care. No such reports were noted in the RemiPCA Network data.[7]

The side effects, risks and benefits and the additional monitoring that has been recommended when using remifentanil for labor analgesia have been widely reported:[5,7,12] its use for labor analgesia is off-label. Of concern, the RemiPCA Network reported a relatively high incidence of neonatal SAE of 1.4% in their study, with 0.3% ultimately attributed to remifentanil use, as well as a high incidence of the need for neonatal oxygen supplementation (7.6%) or bag/mask ventilation (4.0%).[7] This has not been described previously with remifentanil PCA in labor; indeed, Murray et al. reported a safer neonatal profile associated with remifentanil than with labor epidural analgesia in their center.[9]

Commonly-used doses of remifentanil PCA range from 10 μg to 50 μg boluses with lock-out periods of one to three minutes. The RemiPCA Network reduced the dose in their SOP in response to literature reports of maternal SAEs with doses greater than 40 μg;[7] and in Belfast, a regimen based on a 40 μg bolus available every two minutes, without a background infusion, is used.[9] Table 1 summarizes dose regimens reported in previous studies.[3–7,13–41] The use of continuous background infusions is rare and has been considered to be associated with respiratory depression more frequently. The dose reduction and the above data imply that a 'safe' dose has been established, but the balance between safety and efficacy is not yet fully established.

Other unresolved areas related to remifentanil use in labor include parturient eligibility criteria, optimal timing in labor to initiate remifentanil PCA, and the duration of administration. Due to opioid tolerance (tachyphylaxis)[42] it is yet to be investigated in the setting of long labor. Some of the earlier studies[12] limited its use to two hours, including in Belfast.[4] The RemiPCA Network reported a median duration of remifentanil use of 3.3 h and 1.8 h for nulliparous and multiparous women, respectively. This is an important point if the aim of women in labor is choosing remifentanil to replace epidural analgesia. Of the 34 published studies, 13 did not report the duration of administration; and 15 did not report the length of labor (Table 1). In a multicenter study in the United Kingdom (UK), the duration of labor, opioid analgesia repeat-doses (meperidine could

Table 1 Remifentanil for labor analgesia; duration of administration and regimens

Study	Study year	No. in remifentanil group	PCA regimen (bolus, rate, lockout)	Initiation of remifentanil	Duration of remifentanil, mean (min)	Duration of labor, mean (min)	Epidural conversion rate (remifentanil group) (%)	Comparison group‡
Olufolabi et al.[37]	2000	4	0.25–0.5 μg, 2–5 min	NR	147*	NR	NR	NR
Volikas et al.[38]	2001	9	0.5 $\mu g.kg^{-1}$, 2 min	Upon request of analgesia	NR	362	11	PCA pethidine
Blair et al.[4]	2001	21	0.25–1.0 $\mu g.kg^{-1}$, 2 min + background infusion 0–0.05 $\mu g.kg^{-1}.min^{-1}$	Cervix >3 cm, established labor	NR	NR	38	NR
Roelants et al.[39]¥	2001	6	25 μg, 5 min + background infusion 0.05–0.075 $\mu g.kg^{-1}.min^{-1}$	Cervix >4 cm, regular contractions	196*	NR	NR	NR
Thurlow et al.[40]	2002	18	20 μg, 3 min	Early labor	NR	NR	39	IM pethidine
Volmanen et al.[41]	2002	17	0.2–0.8 $\mu g.kg^{-1}$, 1 min	Cervix <7 cm, first stage	60 β	NR	NR	NR
Evron et al.[13]	2005	43	20–70 μg, 3 min	Upon request of analgesia	NR	283*	11	PCA pethidine
Blair et al.[14]	2005	20	40 μg, 2 min	Upon request of analgesia	148	282*	NR	PCA pethidine
Volikas et al.[15]	2005	50	0.5 $\mu g.kg^{-1}$, 2 min	Upon request of analgesia	NR	539	14	NR
Volmanen et al.[36]	2005	15	0.4 $\mu g.kg^{-1}$, 1 min	Cervix <7 cm, first stage	NR	NR	NR	Nitrous oxide
Rabie et al.[16]	2006	15	0.4 $\mu g.kg^{-1}$, 1 min	Cervix >3–6 cm, active labor	NR	569	NR	Epidural
Shahriari et al.[17]	2007	20	25–50 μg, 4 min	Cervix >3–5 cm, pain >6, upon request	NR	160	NR	IM pethidine
Balki et al.[18]	2007	20	0.25–1.0 $\mu g.kg^{-1}$, 2 min + background infusion 0.025–0.1 $\mu g.kg^{-1}.min^{-1}$	Upon request of analgesia	388	NR	5	PCA remifentanil
Volmanen et al.[19]	2008	24	0.1–0.9 $\mu g.kg^{-1}$, 1 min	First stage	60 β	NR	NR	Epidural
Douma et al.[3]	2010	52	40 μg, 2 min	Active labor	234	399*	13	Fentanyl or pethidine
Ng et al.[20]	2011	34	25–30 μg, 3.75–4.5 min	Upon request of analgesia	NR	NR	NR	IM pethidine
Douma et al.[21]	2011	10	40 μg, 2 min	Cervix <5 cm, active labor	286	559*	10	Epidural
Marwah et al.[22]§	2012	47	0.25 $\mu g.kg^{-1}$, 2 min + background infusion 0.025 $\mu g.kg^{-1}.min^{-1}$	NR	318	NR	6	PCA fentanyl
Ismail et al.[23]	2012	380	0.1–0.9 $\mu g.kg^{-1}$, 1 min	Cervix <3 cm, 2 in 10 contractions, upon request of analgesia	618	627*	NR	Epidural or CSE
Tveit et al.[24]	2012	17	0.15–0.6 $\mu g.kg^{-1}$, 2 min	Cervix >2 cm, regular contractions	225	411*	11	Epidural
Shen et al.[25]	2013	27	0.1–0.4 $\mu g.kg^{-1}$, 2 min	Cervix 1–3 cm	NR	NR	7	Remifentanil continuous infusion

Tveit et al.[26]	2013	41	0.15–1.0 μg.kg^{-1}, 2 min	Ongoing contractions, cervix >3 cm	216	391*	7	NR
Jost et al.[26]	2013	23	20–55 μg, 2 min + background infusion 50 μg.hour^{-1}	Cervix >2 cm, contractions <5.min^{-1}, pain score >5	89	308 α	NR	PCA remifentanil (60 μg bolus with rate decrease)
Stocki et al.[5]	2014	19	20–60 μg, 2 min	Cervix >2 cm, upon request of analgesia	NR	364*	16	Epidural
Stourac et al.[27]	2014	12	20 μg, 3 min	Upon request of analgesia	163	272*	NR	Epidural
Lin et al.[28]§	2014	170	0.4 μg.kg^{-1}, 5 min + background infusion 0.04–0.05 μg.kg^{-1}.min^{-1}	NR	172	NR	NR	Epidural
Freeman et al.[29]	2015	447	20–40 μg, 3 min	Upon request of analgesia	236	20#	13	Epidural
Douma et al.[30]	2015	49	40 μg, 2 min	Cervix <7 cm, upon request of analgesia	192	390 α	17	Epidural or control
Frauenfelder et al.[31]	2015	166	30 μg, 1 min + background infusion 80–120 μg.h^{-1}	Cervix >2 cm, upon request of analgesia	NR	NR	15	Epidural
Messmer et al.[32]	2016	61	20–50 μg, 1 min	Requesting remifentanil PCA	NR	NR	23	NR
Logtenberg et al.[33]	2017	81	20–40 μg, 3 min	Upon request of analgesia	261	33#	15	Epidural
Leong et al.[34]¥	2017	29	20–50 μg, 2 min + background infusion 0.00–0.1 μg.kg^{-1}.min^{-1}	Upon request of analgesia	348	25#	3	NR
Wilson et al.[6]	2018	201	40 μg, 2 min	Established labor, upon request of analgesia	NR	NR	19	IM pethidine
Melber et al.[7] RemiPCA Network	2019	5740	10–30 μg, 2 min	NR	Nullipara: 198 Multipara: 108	NR	21	NR

All studies were prospective unless otherwise noted. §: retrospective study. ¥: case series. Remi: remifentanil. ‡: intravenous opioid or neuraxial technique unless otherwise stated. IM: intramuscular.: PCA: patient-controlled analgesia. CSE: combined spinal-epidural. NR: not reported. *: calculated mean. #: second stage only. α: time from admission to delivery. β: study period.

be administered every four hours) and cumulative opioid doses were not reported; thus it is unclear how long opioid analgesia remained effective.[6]

Since 2004, the Belfast center has offered laboring women a menu of analgesic methods, including remifentanil PCA, other IM opioids and labor epidural analgesia. The availability of remifentanil has generated a substantial reduction in the use of epidural analgesia in their center from 41% to 25%.[9] The UK multicenter study randomized women to receive either remifentanil PCA or IM pethidine.[6] Once randomized, women were free to choose whether to continue with the allocated opioid or to request epidural analgesia at any time during labor. No woman randomized to receive remifentanil requested immediate provision of epidural analgesia and overall only 19% assigned to remifentanil PCA received epidural analgesia.[6] A recent commentary in the British Medical Journal suggested that widespread remifentanil use may halve the rate of epidural analgesia for labor.[43]

Women may not intend to receive labor epidural analgesia and furthermore, they may be disappointed if this is the only analgesic option available. Orbach-Zinger et al. reported that women with unmet expectations regarding labor epidural analgesia provision had a higher rate of postpartum depression.[44] A population database of over two million deliveries in 2015 in the United States identified statewide variations in labor epidural analgesia use, however, the authors were unable to identify whether these variations were due to lack of epidural services or patient choice.[45] Ideally, women should know all the labor analgesia options available in the center where they choose to deliver, including labor epidural analgesia and the alternatives.

We would contend that our goal as obstetric anesthesiologists is not to replace labor epidural analgesia completely with alternative analgesic techniques. Anesthesia-related maternal mortality has decreased inversely to increased use of labor epidural analgesia.[46] One possible consequence of freely-available alternative analgesia is the potential for increased use of general anesthesia for cesarean delivery or postpartum procedures.[47] Thus, some criteria for assessing women who may request remifentanil PCA rather than epidural analgesia are needed to enable identification of high-risk women for whom an epidural may be preferable. For example, women undergoing a trial of labor after cesarean with risk factors predicting a difficult airway;[48] or with significant comorbidities such as obesity and cardiac disease, may be advised that labor epidural analgesia could be a better option. It is important to remember that maternal choice of pain relief in labor is based on many factors and the opinion of clinicians is only one for them to consider.

Currently, remifentanil PCA is not a universally available choice as a method of labor analgesia, much as twilight labor anesthesia was only available to select women in the early 20th century.[49] Imagine a future in which predictors of labor pain would be robust[50] and women would know what level of analgesia they might require, in conjunction with their risks of comorbidity and of cesarean delivery. The à la carte menu currently available only to the discerning and lucky minority could become a buffet of choices, liberally available to all laboring women.

The three studies presented in this volume of IJOA provoke important questions regarding remifentanil PCA as an approach to labor analgesia. However, before we can confidently support the widespread use of remifentanil PCA in this setting, there is a need for more research in order to understand the maternal and neonatal efficacy and safety outcomes in high-risk laboring women, and to explore further the respiratory effects of remifentanil in labor. Other lingering questions include the optimal time to initiate remifentanil administration and the expected duration of effective pain relief as labor progresses. Choice is desirable for labor analgesia but strict safety guidelines must be adhered to when remifentanil is used because of the potential dangers.

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