Neuraxial analgesia: a review of its effects on the outcome and duration of labor

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Labor pain is one of the most challenging experiences encountered by females during their lives. Neuraxial analgesia is the mainstay analgesic for intrapartum pain relief. However, despite the increasing use and undeniable advantages of neuraxial analgesia for labor, there have been concerns regarding undesirable effects on the progression of labor and outcomes. Recent evidence indicates that neuraxial analgesia does not increase the rate of Cesarean sections, although it may be associated with a prolonged second stage of labor and an increased rate of instrumental vaginal delivery. Even when neuraxial analgesia is administered early in the course of labor, it is not associated with an increased rate of Cesarean section or instrumental vaginal delivery, nor does it prolong the labor duration. These data may help physicians correct misconceptions regarding the adverse effects of neuraxial analgesia on labor outcome, as well as encourage the administration of neuraxial analgesia in response to requests for pain relief. (Korean J Anesthesiol 2013; 65: 379-384)

Key Words: Analgesia, Cesarean section, Neuraxial, Obstetric labor.

Introduction

Labor pain is one of the most challenging experiences encountered by females during their lives. Painful labor produces maternal physiological changes that may affect maternal and fetal wellbeing. The maternal catecholaminergic surge in norepinephrine and epinephrine in response to labor pain increases maternal oxygen consumption, which may lead to incoordinate uterine action, consequently causing decreased placental perfusion. In some cases, increased maternal oxygen consumption may be deleterious to maternal and fetal health. In addition, maternal hyperventilation in response to labor pain causes adverse effects such as reduced fetal oxygen delivery [1,2]. Besides these acute maternal and fetal hemodynamic and metabolic responses, intense labor pain has been correlated with the development of postpartum posttraumatic stress [3], postpartum depression, and persistent pain [4].

Neuraxial analgesia is the most effective technique for pain relief during labor. Numerous studies comparing neuraxial analgesia with systemic opioids or other techniques have demonstrated the superior pain relief and maternal-fetal physiologic benefits of neuraxial analgesia [5-9]. Furthermore, Hiltunen et al. [10] reported that neuraxial analgesia could reduce the risk of immediate postpartum depression. As a result of the advantage

of neuraxial analgesia, its use for labor analgesia has increased continuously over the past several decades. In the United States, the use of neuraxial analgesia has tripled from 22% in 1981 to 61% in 2001 [11]. In recent studies including those of Harkins et al. [12] and the Le Ray et al. [13], the rate of neuraxial analgesia administration reached 75–80% of all women in labor.

However, since the introduction of neuraxial analgesia into the labor analgesia field, there has been controversy regarding its effects on the obstetric outcome. While early observational studies suggested that neuraxial analgesia caused a higher incidence of adverse effects on labor outcome, recent evidence no longer supports these historic beliefs. Nevertheless, a number of misconceptions regarding the effects of neuraxial analgesia on the labor outcome still hamper its timely use in obstetric practice. In fact, one of the major reasons offered by patients for refusing neuraxial analgesia is concern about its possible interference with the course and outcome of labor [12,14-16]. Therefore, anesthesiologists should provide correct, up-to-date information regarding the effects of neuraxial analgesia on the labor outcomes for patients seeking labor pain relief.

This review summarizes the current research regarding the effects of neuraxial analgesia on labor, focusing on associations between neuraxial analgesia and the incidence of Cesarean and instrumental vaginal delivery, the duration of labor, as well as the impact of the type or administration time of neuraxial analgesia on the outcome of labor.

Neuraxial Analgesia and Labor Outcome

Observational studies

Observational studies are designed such that the researcher naturally observes subjects and measures variables without assigning treatments to the subjects. Therefore, observational studies have high external validity because they reflect actual clinical labor practices without any intervention (no selection bias, no treatment crossover).

In early observational studies, neuraxial analgesia appeared to be associated with prolonged labor times and increased rates of Cesarean sections and instrumental vaginal deliveries. These observations developed into a longstanding belief among obstetric providers that neuraxial analgesia delays labor and leads to increased rates of Cesarean sections and instrumental vaginal deliveries. However, interpretation of these studies is complex because of the presence of numerous confounding factors that can adversely affect labor outcome and patient selection bias [17]. For example, patients with complicated labor are more likely to experience severe pain, thus requiring more analgesics. These patients may consequently be more likely to choose neuraxial analgesia than patients with uncomplicated labor. Patients with

a complicated labor may independently have a higher incidence of Cesarean section and instrumental delivery. In fact, Hess et al. [18] addressed this issue by investigating the association between severe labor pain and rates of Cesarean section. Patients who experienced three or more episodes of breakthrough pain during low-dose epidural bupivacaine/fentanyl labor analgesia had higher rates of Cesarean section in comparison to patients who experienced less pain (odds ratio 2.6, 95% CI 2.0 to 3.4). As such, patients' requests for analgesia might represent a marker of other comorbid risk factors for Cesarean section (e.g., dysfunctional labor, macrosomia, and malpresentation). Observational studies are not capable of reliably indicating whether neuraxial analgesia increases the risk of Cesarean section or instrumental vaginal delivery.

Impact studies

Impact studies are used to determine how a certain treatment affects patient outcomes. Known as sentinel event studies or before-after studies, these studies are designed to compare the incidence of patient outcomes before and after a sentinel event (e.g., introduction of a neuraxial analgesia in labor). This study design excludes cross-over between treatment groups and patients do not choose to participate in the study. Therefore, this study design provides high external validity. However, changes in hospital management and policies, or in patients' characteristics in the before and after treatment time periods, can influence the outcome [19].

In a large study, Yancey et al. [20] investigated the impact of the administration of neuraxial analgesia on Cesarean section at the Tripler United States Army Hospital before and after 1993. As a result of the availability of neuraxial labor analgesia in 1993, the rate of epidural analgesia increased from 1 to 80% over 1 year. Despite this increased rate of neuraxial analgesia, the incidences of Cesarean sections (19.0 vs. 19.4%) and instrumental vaginal deliveries (11.1 vs. 11.9%) remained unchanged. Another observational study investigating this topic was conducted in the National Maternity Hospital in Dublin, Ireland. Here, Impey et al. [21] compared the obstetric consequences, using retrospective analysis, of 1,000 nulliparous females in spontaneous labor at term who delivered in 1987 with comparable groups who delivered in 1992 and 1994 at the same hospital. Cesarean section (4% in 1987, 5% in 1992, and 4% in 1994) and instrumental vaginal delivery rates remained unchanged, although the epidural analgesia rate increased during this time period (10% in 1987, 45% in 1992, and 57% in 1994). A meta-analysis including nine impact studies involving 37,753 women was conducted by Segal et al. [22]. There were no significant increases in the rate of Cesarean section (mean change 0.67%, 95% CI 2.0 to 0.74) or instrumental vaginal delivery (mean change 0.76%, 95% CI 1.2

to 2.8) before and after the implementation of neuraxial analgesia.

Randomized controlled studies

Randomized controlled trials are the gold standard design of clinical trials and are used to test the outcome of medical interventions. However, in addition to their limitations, including low external validity and low sample sizes, randomized controlled trials have several weaknesses in the labor analgesia field. For example, neuraxial analgesia has superior analgesic effects in comparison to other forms of analgesia. Also, the use of randomized controlled study designs in the labor analgesia field includes potential limitations such as not including a placebo group or blinding, and higher cross-over rates. Nonetheless, several randomized controlled trials and meta-analyses have compared the effects of neuraxial analgesia to non-neuraxial analgesia on labor outcome. Sharma et al. [23] conducted an individual patient meta-analysis (n = 2,703) comparing Caesarean section rates in female patients randomized to epidural analgesia or systemic opioid analgesia. Their results suggested that the administration of neuraxial analgesia does not increase the risk of Cesarean section (odds ratio 1.04, 95% CI 0.81 to 1.34). A 2011 meta-analysis of 38 randomized trials comparing all modalities of epidural (including combined-spinal-epidural), non-epidural analgesia, and no analgesia during labor concluded that epidural analgesia did not significantly increase the risk of Cesarean section (RR 1.10, 95% CI 0.97 to 1.25). Further, the majority of studies (n = 33) compared epidural analgesia with systemic opioids. Five of the included studies compared epidural analgesia with no analgesia during labor [5]. Thus, results of randomized controlled trials and meta-analyses of these trials strengthen the conclusion that neuraxial analgesia does not increase the rate of Cesarean section deliveries.

In contrast, systematic reviews of randomized controlled trials comparing neuraxial analgesia to systemic opioid analgesia conclude that neuraxial analgesia is associated with an increased risk of instrumental vaginal delivery. In an individual patient meta-analysis (n = 2,703) reported by Sharma et al. [23] and a 2004 meta-analysis (n = 2,962) by Liu and Sia [24], the adjusted odds ratios for instrumental vaginal delivery were 1.86 (95% CI 1.43 to 2.40) and 1.63 (95% CI 1.12 to 2.37), respectively. Similarly, a meta-analysis in 2011 demonstrated that neuraxial labor analgesia was associated with an increased risk of instrumental vaginal birth (RR 1.42, 95% CI 1.28 to 1.57) [5]. However, the cause of the increased rate of instrumental delivery in patients with neuraxial analgesia is uncertain. One possible explanation is that the presence of epidural analgesia engenders a difference in obstetric management [25,26]. For example, the relaxation of the abdominal wall muscles secondary to neuraxial analgesia could encourage the use of instrumental deliveries. Also, there

were significantly more instrumental deliveries in teaching hospitals for patients administered epidurals, which could have been a result of instructing residents how to perform instrumental vaginal deliveries.

The effects of neuraxial analgesia on the duration of the first stage of labor were varied, as neuraxial analgesia prolongs the second stage of labor. A 2005 Cochrane review found no difference in the duration of the first stage of labor among patients administered epidural analgesia versus those with systemic opioid or no analgesia [27]. However, the individual meta-analysis of studies by Sharma et al. [23] demonstrated that the first stage of labor is prolonged by approximately 30 min in nulliparous patients with epidural analgesia. Cambic and Wong [19] speculated that these inconsistent results are likely a result of variations in the frequency of cervical examination or the impact of confounding factors such as fluid blouses, which can influence uterine activity. A 2011 Cochrane review concluded there was no difference in the duration of the first stage of labor (mean difference 18.51 min, 95% CI 12.91 to 49.92; 11 trials, 2,981 patients). However, the second stage of labor was longer (mean difference 13.66 min, 95% CI 6.67 to 20.66; 13 trials, 4,233 patients) in those receiving neuraxial analgesia compared to those receiving systemic opioids or no analgesia [5]. It appears that the magnitude of prolonged labor has no clinical significance. In fact, several studies showed that a prolonged duration of the second stage of labor is not associated with maternal or fetal morbidity so long as the fetal status is within normal limits, the mother is well hydrated with adequate analgesia, and there is progress in fetal head descent [28-30].

In summary, much evidence suggests that neuraxial analgesia does not increase the frequency of Cesarean section deliveries in comparison to systemic opioids. There is, however, conflicting evidence with regard to instrumental delivery rates. Whereas randomized controlled trials have concluded that neuraxial analgesia is associated with an increased risk of instrumental vaginal birth, impact studies have identified no such difference. Neuraxial analgesia prolongs the second stage of labor; however, this appears to be of no clinical significance.

The Type of Neuraxial Analgesia and Labor Outcome

The use of the combined spinal epidural (CSE) techniques for labor analgesia has become popular in recent years as a consequence of its faster onset of analgesia in comparison to a standard epidural.

An early study by Tsen et al. [31] suggested that CSEs, when compared to a standard labor epidural, might reduce the rate of cervical dilation (2.3 vs. 1.3 cm/h, respectively; P = 0.0154) and the duration of labor. However, large clinical trials and the

Cochrane review found no difference in the labor outcome or duration of labor. A randomized trial including 2,183 patients by Norris et al. [32] revealed no difference in labor outcome or the duration of the first or second stage of labor between analgesic techniques. Another large trial, the COMET study [33,34], randomly assigned more than 1,000 female patients to one of three groups: traditional epidural (intermittent boluses of 0.25% bupivacaine); low dose epidural (continuous infusion of bupivacaine 0.1% and fentanyl 2 mg/ml); or low-dose CSE (intrathecal bupivacaine 2.5 mg/fentanyl 25 mg, followed by intermittent boluses of bupivacaine 0.1% and fentanyl 2 mg/ml). The CSE and low-dose epidural groups had lower rates of instrumental delivery compared to the traditional epidural group. However, there was no difference between the CSE and low-dose epidural groups. The incidence of Cesarean section and the duration of the first or second stage of labor were not different among three groups.

A 2012 meta-analysis enrolled 3,303 female patients in a study comparing the effects of CSE versus epidural analgesia on labor. The first group involved all CSE variants versus traditional epidurals, and the second group included all CSE variants versus low-dose epidurals and variants. CSE was associated with fewer instrumental vaginal deliveries than the traditional epidural group (RR 0.80, 95% CI 0.67 to 0.97; six trials, 1,015 patients). However, no significant difference was found in instrumental vaginal delivery between CSE and low-dose epidural (RR 1.07, 95% CI 0.88 to 1.30; 11 studies, 1,612 patients). There was no significant difference in the incidence of Cesarean section for any of the comparisons: CSE vs. traditional epidural (RR 1.04, 95% CI 0.84 to 1.30; six studies, 1,015 patients); or CSE vs. low dose epidural (RR 0.97, 95% CI 0.82 to 1.16; 15 trials, 1960 patients) [35].

In conclusion, there were no differences in mode of delivery or labor duration with CSE compared to low-dose epidural.

The Timing of Neuraxial Analgesia and Labor Outcome

The American College of Obstetricians and Gynecologists (ACOG) maintained for many years that a patient's request for epidural analgesia should be delayed, if possible, until the cervix is dilated to 4−5 cm [36]. This recommendation is based on observational studies suggesting an association between Cesarean section and the use of neuraxial analgesia during early labor [37,38]. Randomized controlled trials have addressed this issue by comparing early epidural analgesia to systemic opioid analgesia. These studies consistently show that early epidural analgesia does not increase the rate of Cesarean section deliveries.

Ohel et al. [39] randomized 449 nulliparous female patients who were in spontaneous and induced labor into either immediate initiation of epidural analgesia at the first request or delay

of the epidural until the cervix was 4-cm dilated. Mean cervical dilations at the beginning of epidural analgesia were 2.4 and 4.6 cm in the early and late epidural groups, respectively. The mean duration of the first stage of labor was slightly shorter in the early group (9.4 vs. 10.3 h, P = 0.04), but there was no difference in the mean duration of the second stage (95.4 vs. 105.2 min, P = 0.12). The investigators found no difference in the incidence of Cesarean section (13 vs. 11%, P = 0.85) or instrumental vaginal delivery (17 vs. 19%, P = 0.63) between the groups.

Wong et al. [40] compared the initiation of early neuraxial analgesia with systemic opioid analgesia. In their randomized trial, 750 nulliparous female patients in spontaneous labor at less than 4-cm cervical dilatation were assigned to receive either intrathecal fentanyl or systemic hydromorphone for the first analgesia request. Subsequently, epidural analgesia was initiated in the intrathecal group at the second request, and in the systemic group at a cervical dilation of 4.0 cm or greater or at the third request for analgesia. At initiation of neuraxial analgesia, the median cervical dilations were 2 and 4 cm in the early and late groups, respectively. No differences were found in the incidence of Cesarean section (17.8 vs. 20.7%, P = 0.31) or instrumental vaginal delivery (19.6 vs. 16.0%, P = 0.13) between the groups. Of interest, the mean total duration of the first stage of labor was slightly shorter in the early group (398 vs. 479 min, P < 0.001), but there was no difference in the mean duration of the second stage (71 vs. 82 min, P = 0.67).

According to these studies, in 2006 the ACOG Committee Opinion concluded that a maternal request is a sufficient medical indication for pain management during labor, and there is no need to withhold analgesia until cervical dilatation reaches 4 cm [41].

Similarly, Wong et al. [42] conducted a subsequent study comparing early to late neuraxial analgesia in 806 nulliparous labor inductions. At initiation of neuraxial analgesia, the median cervical dilations were 3 and 4 cm in the early and late groups, respectively. The investigators found no difference in the incidence of Cesarean sections (32.7 vs. 31.5%, P = 0.65) or instrumental vaginal deliveries (20.9 vs. 21.5%, P = 0.63) between the groups. Of note, the mean total duration of the first stage of labor was slightly shorter in the early group (528 vs. 569 min, P = 0.047), but there was no difference in the mean duration of the second stage of labor (89 vs. 90 min, P = 0.56).

A large randomized controlled study by Wang et al. [43] enrolled 12,793 nulliparous female patients who were randomly assigned to receive early epidural analgesia (at the women's first request if cervical dilation was ≥1 cm) compared with late epidural analgesia (systemic meperidine until a cervical dilation ≥ 4 cm was reached). At initiation of neuraxial analgesia, the median cervical dilation was 1.6 cm in the early group and 5.1 cm in the late group. The authors reported no increase in Cesar-

ean section (23.2 vs. 22.8%, P = 0.51) and instrumental delivery rates (11.8 vs. 12.7%, P = 0.1) in the early group when compared with the late group despite the exceptionally early initiation of epidural analgesia. Additionally, there was no difference in the duration of the total (11.3 vs. 11.8 h, P = 0.9) or second stages (63 vs. 67 min, P = 0.87) of labor.

A 2011 meta-analysis of five randomized trials and one retrospective cohort study (n = 14,836) indicated that early administration of neuraxial analgesia (cervical dilation ≤ 3 cm) did not increase the incidence of Cesarean sections (RR 1.02, 95% CI 0.96 to 1.08) or instrumental deliveries (RR 0.96, 95% CI 0.89 to 1.05) in comparison to later administration (cervical dilation ≥ 4 cm) [44].

To summarize, in randomized controlled trials comparing early to late neuraxial analgesia, there was no increase in the rate of Cesarean section or instrumental vaginal delivery. Also, early neuraxial analgesia does not prolong the duration of labor in comparison to late neuraxial analgesia.

Conclusion

Recent large-scale studies and reviews showed that neuraxial labor analgesia does not increase the risk of Cesarean section when compared with systemic or no analgesia. Additionally, early administration of neuraxial analgesia does not increase the rate of Cesarean sections or instrumental vaginal deliveries, nor does it prolong the duration of labor. This updated information may correct widely held misconceptions regarding the adverse effects of neuraxial analgesia on labor outcomes, thereby encouraging physicians to promote active administration of neuraxial analgesia in response to patients' requests for pain relief.

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