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Labour analgesia effects on foetal heart rate. A mini-review

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ABSTRACT

Foetal well-being during labour is of utmost importance. One of the ways to attempt to assess foetal well-being is by recording foetal heart rate (FHR). Loss of variability and deceleration patterns are known to be associated with foetal distress. Decelerations and foetal bradycardia have been described after any type of effective labour analgesia. This review addresses the questions if certain analgesic techniques and/or analgesics lead to clinically relevant FHR changes, what is their aetiology, and how we should manage these FHR changes.

Keywords: Labour Analgesia, Foetal Heart Rate Changes, Epidural Analgesia, Combined Spinal Epidural, Intravenous Analgesia

1. INTRODUCTION

Foetal well-being during labour is of utmost importance. One of the ways to attempt to determine foetal well-being is by recording foetal heart rate (FHR). Loss of beat to beat variability and deceleration patterns are known to be associated with foetal distress. Gynaecological factors, maternal and foetal factors, but also anaesthesiological factors can influence these FHR tracings. Decelerations and foetal bradycardia have been described after all types of effective labour analgesia (epidural, spinal and Combined Spinal Epidural (CSE), and intravenous opioids).

Early descriptive reports were conflicting. Lieberman *et al*. [1] compared intramuscular meperidine to epidural bupivacaine and only detected significant FHR changes in parturients with hypotension or uterine hyper stimulation. In contrast, Boehm *et al*. who studied epidural lidocaine with or without epinephrine, found that 53% (eight patients) revealed a reduction in FHR variability without indication of the exact mechanism [2]. Later studies failed to demonstrate these effects of epidural lidocaine with or without epinephrine [3,4]. Unfortunately these studies are difficult to interpret because of a lack of randomization, small sample sizes and inconsistent dose schemes.

This mini-review provides a comprehensive intrapartum data on FHR effects of a multitude of analgesic regimens which makes it different from previously published reports. It attempts to address the questions if certain techniques and/or analgesics lead to clinically relevant FHR changes, such as loss of baseline variability, late decelerations or severe variable deceleration patterns, what is their aetiology, and how we should manage these FHR changes.

2. METHODS

A MEDLINE-based search of all the literature on FHR changes due to labour analgesia was performed. The following keywords were used: labour analgesia; foetal heart rate changes; epidural analgesia; combined spinal epidural; intravenous analgesia; and acupuncture. No date or language restriction was used. The reference lists of retrieved articles were searched by hand. Articles that did not report on the FHR outcomes were excluded. In this mini-review, no meta-analysis was performed.

3. EPIDURAL ANALGESIA

Continuous epidural analgesia is commonly used for analgesic treatment during labour and delivery as it effectively relieves labour pain. In reviewing the literature many reports about changes in FHR in labouring patients with epidural analgesia were found. Historically abnormal FHR patterns have been found to be most common when epidural analgesia was accompanied by maternal hypotension [5], or supine position of the parturient [6]. Stavrou *et al*. [7] conducted a retrospective study trying to find a relationship between prolonged foetal bradycardia and epidural analgesia during labour. They concluded that administration of epidural analgesia is associated with episodes of prolonged foetal bradycardia, as they found that prolonged bradycardia (defined as a fall in

FHR at least 50/min below baseline and lasting at least 3 minutes) developed in 40 of 366 (11%) of parturients with epidural analgesia. These FHR changes were not accompanied by maternal hypotension (hypotension occurred only in one patient) and FHR returned to normal in all patients. Most episodes of foetal bradycardia occurred within 20 minutes of local anaesthetic administration. Neonatal outcome was not influenced.

Another retrospective comparative study between patients with and without epidural analgesia showed significant differences in variable decelerations and late decelerations in FHR tracing before and after institution of epidural analgesia. An increase in variable and late decelerations was observed after injection of the main dose of epidural analgesic. Twenty four percent of cardiotocograph tracings (CTGs) showed variable decelerations before, and 35% showed decelerations after epidural analgesia [8]. Neonatal outcome was similar in both groups. As mentioned by the authors, groups were perhaps not comparable as the epidural group contained more primipara, more frequent induction of labour, first and second stages of labour were longer (possibly an effect of the epidural) and the duration of ruptured membranes was longer. The authors suggest that these FHR changes might be attributed to direct effects of the local anaesthetic on the foetus. However, Phillips *et al*. [9] studied PR interval, RR interval, T/QRS ratio and the PR-RR correlation coefficient using foetal electrocardiogram waveform analysis during epidural analgesia with bupivacaine and found a significant increase in FHR and a fall in T/QRS ratio. Their conclusion was that epidural bupivacaine does not alter foetal myocardial conduction as measured by PR interval nor does it induce ischemic cardiac changes as assessed by the T/QRS ratio. Thus the FHR changes occurring during epidural analgesia are not caused by a direct depression of the foetus by bupivacaine.

During the last fifteen years, the addition of opioids to local anaesthetics for epidural analgesia has become increasingly popular because it offers the advantage of reduction of the local anaesthetic dose with faster onset of analgesia and resulting in the same amount of analgesia than with local anaesthetics alone [10]. Dose reduction of local anaesthetic results in less motor blockade which can allow for ambulation during labour, and may reduce the risk of dystocia and caesarean section. Purported advantages of ambulation consist of increased intensity of contractions, less pain, shorter first stage of labour, and patient's appreciation of mobility [10]. Studies on the effect of ambulation on labour have not shown any detrimental effects [11,12]. Hoffman *et al*. studied the effects of continuous opioid epidural on FHR but without letting the parturient ambulate. They discovered that there are no significant differences between opioid and non-opioid epidurals with respect to maternal blood pressure, FHR tracings, and neonatal outcome [10]. These results were confirmed by a double blind, randomized, controlled study, by Amant and co-workers [13], 109 parturients who received bupivacaine 0.25% with addition of either butorphanol, fentanyl, sufentanil or saline.

Prophylactic administration of ephedrine to prevent maternal hypotension and FHR changes has also been studied. In a prospective randomised trial by Kreiser *et al*. [14], 145 parturients were scheduled to either receive ephedrine 10 mg i.v. bolus followed by a continuous infusion of 20 mg i.v. during one hour at time of initiation of the epidural analgesia, or no prophylactic ephedrine. FHR monitoring was used during the first 40 minutes after anaesthetic administration. The analgesic dose in this study was relatively high (3 ml of 2% lidocaine for initiation, followed by 8 ml of bupivacaine 0.25%). FHR changes occurred in 2 out of 72 treated patients and in 11 of 73 controls. In another randomised trial Cleary-Goldman *et al*. [15] studied the effects of intramuscular ephedrine 25 mg versus placebo in 100 parturients treated with CSE analgesia. Significantly fewer women in the ephedrine group developed hypotension. There were no differences in FHR decelerations in the hour following initiation of analgesia. There was however an increased risk for development of foetal tachycardia in the group treated with ephedrine.

Prophylactic use of ephedrine does not seem indicated for low dose labour analgesia ("walking epidural"). Continuous infusion of ephedrine is not recommended because it has been associated with foetal acidosis in cases of elective caesarean section [16].

Studies conducted on epidural opioids alone gave different results. Capogna and co-workers [17] conducted a prospective, sequential allocation study to determine the minimum effective concentration of epidural sufentanil in spontaneous and induced labours. A transient reduction (mean 30 minutes) of FHR long-term variability was found in 53% of spontaneous and in 63% of induced labours within 10 minutes of administration of epidural sufentanil 18 µg - 32 µg. All FHR changes resolved sponta- neously. According to the authors one explanation for these FHR changes could be a direct depressant effect of opioids as was determined for morphine and pethidine by Petrie *et al*. [18]. Although epidural sufentanil in therapeutic doses (10 µg - 30 µg of sufentanil in the epidural mixture) is detectable in the maternal circulation [19], it seems unlikely that these low doses used for epidural analgesia have any important systemic impact [19,20].

4. INTRATHECAL OPIOIDS, COMBINED SPINAL-EPIDURAL ANALGESIA (CSE)

Combined spinal epidural (CSE) analgesia has become

increasingly popular as a method for labour pain relief as it has a very rapid onset of analgesia. FHR changes have been observed with intrathecal analgesia using small doses of local anaesthetic or opioids, alone or in combination.

At first, the increase in variable decelerations noted in a prospective, double blind, comparative study among intrathecal fentanyl, meperidine, and sufentanil by Honet *et al*. [21], was deemed to be of little clinical significance.

Two years later however Clarke and co-workers reported several episodes of uterine hyperactivity in some cases associated with foetal bradycardia following intrathecal administration of 50 µg of fentanyl [22]. A decrease in foetal heart rate to 80 - 100 beats/min was noted in 7 of 30 consecutive patients. In two other patients the foetal heart rate decreased below 70 beats/min. These FHR alterations occurred without maternal hypotension and all appeared within 30 minutes after intrathecal injection of fentanyl. Five out of the nine patients with foetal bradycardia also exhibited uterine hyperactivity detected by external or internal pressure transducer. This uterine hyperactivity following intrathecal fentanyl has since been confirmed on several occasions [23-25].

Yet there is no agreement about the association between uterine hyperactivity and non-reassuring FHR patterns caused by spinal opioids.

Gambling *et al*. [26] conducted a large randomized trial comparing i.v. meperidine with CSE (with intrathecal sufentanil 10 µg) and reported FHR decelerations in 18% in the CSE group compared to 21% in the meperidine group. However bradycardia necessitated caesarean section in 8 out of 400 women with CSE compared to 0 out of 352 mothers in the meperidine group. Cautious interpretation of these results is necessary. The mothers who received i.v. meperidine had intermittent FHR monitoring, while the mothers with CSE had continuous monitoring of FHR for at least 30 minutes after intrathecal injection. Furthermore these results are not corroborated by later studies. Eberle and co-workers concluded that the risk of prolonged foetal deceleration after epidural bupivacaine or intrathecal sufentanil labour analgesia is unrelated to analgesic technique [27]. Fogel *et al*. also failed to demonstrate significant differences in the incidence of new prolonged decelerations or late decelerations between epidural and CSE analgesia [28].

In a prospective study by Nielsen *et al*. [29] a comparison was made between the incidence of intrapartum FHR abnormalities and obstetric outcome after epidural bupivacaine and intrathecal sufentanil. The authors conclude that in both groups there was a significantly higher risk of caesarean section in patients who's previously normal FHR tracing became abnormal after analgesia when compared to patients without a new onset FHR abnormality. These new onset FHR abnormalities might be due to a pre-existing problem. However intrathecal sufentanil was not associated with a higher incidence of new onset FHR abnormalities.

In a review article by Norris [30], the author concludes that there is insufficient evidence to accept that spinal opioids are responsible for a more frequent occurrence of new FHR abnormalities when compared to conventional epidural analgesia.

On the other hand there are reports by Van de Velde *et al*. [31] who performed a retrospective analysis on the FHR effects by sufentanil 7.5 µg intrathecally, compared to conventional epidural and compared to sufentanil 1.5 µg intrathecally during CSE. They conclude that sufentanil in a dose of 7.5 µg has the potential to result in more non-reassuring foetal heart rate tracings compared to both other groups.

A systematic review of intrathecal opioids compared with other neuraxial techniques concluded that despite an increased risk for foetal bradycardia: odds ratio 1.8 (95% confidence interval 1.0 to 3.1) the risk for subsequent caesarean section is not increased [32].

More recently Abrao and co-workers [33] performed a randomized controlled trial on 77 parturients to estimate the effects of combined spinal-epidural and traditional epidural analgesia on uterine basal tone and its association with the occurrence of FHR abnormalities. This is the only study in which intrauterine pressure was directly prospectively measured. Patients in the CSE group received bupivacaine 2.5 mg plus sufentanil 2.5 µg. In the epidural group patients received bupivacaine 12.5 mg of a 0.125% solution plus of sufentanil 10 µg. The type of analgesia was shown to be the only independent predictor of uterine hyper tonus. The authors concluded that CSE is associated with a significantly greater incidence of FHR abnormalities related to uterine hyper tonus compared with epidural analgesia, but this did not lead to a higher incidence in caesarean section.

In comment of this study by Abrao and co-workers [33], Landau *et al*. [34] state that the two analgesic regimens used in this study may not be equipotent as shown by the higher pain scores in the epidural group compared to the CSE group. Also the slower onset of pain relief with epidural analgesia makes it likely that FHR and intrauterine tone changes only become apparent after the study period of fifteen minutes. This may have exaggerated the differences reported between study groups. Landau *et al*. also comment on the late initiation of labour analgesia in this study (6 cm cervical dilation) as it is known that neuraxial analgesia in this stage of labour is more commonly associated with FHR abnormalities

than when it is initiated earlier [35]. FHR changes and abnormalities may also be influenced by parity and use of oxytocin which are not adequately detailed in the study by Abrao and co-workers [33].

The 2.5 µg of sufentanil for intrathecal analgesia in the study by Abrao *et al*. [33] is also substantially higher than the dose in group 2 used earlier by Van de Velde and co-workers [36] in a double-blind, double placebo-controlled trial comparing two forms of CSE with epidural analgesia. In this study a comparison was made between epidural bupivacaine 12.5 mg plus 7.5 µg sufentanil 7.5 µg with epinephrine 12.5 µg, intrathecal bupivacaine 2.5 mg plus sufentanil 1.5 µg with epinephrine 2.5 µg, and a third group with sufentanil 7.5 µg intrathecally. Twenty four % of the patients in the high dose intrathecal sufentanil group developed FHR abnormalities compared to 11% in the lower dose intrathecal sufentanil and 12% in the epidural group. Uterine hyperactivity occurred in 12% of the high dose intrathecal sufentanil group compared to 2% in the other two groups, but tocolytic therapy was rarely needed.

The data from these recent studies warrant caution in the use of higher doses of opioids intrathecally because of the risk of uterine hyperactivity and FHR abnormalities, without however increasing the risk for caesarean delivery or detrimental effects on neonatal outcome.

One study has been done with addition of intrathecal tramadol to CSE analgesia. Since there is no human toxicology available for intrathecal administration of tramadol, such studies ethically need to be conducted under specific approval from the appropriate government source. Frikha *et al*. [37] conducted a randomized prospective study comparing bupivacaine 2.5 mg with sufentanil 2.5 µg to bupivacaine 2.5 mg with tramadol 25 mg intrathecally. The purpose of this study was to compare tramadol and sufentanil in terms of duration of analgesia and frequency of adverse maternal or foetal effects. FHR tracings of all patients were done from one hour before analgesia to one hour after initiation of analgesia. All FHR tracings were normal before initiation of CSE. FHR tracings after initiation of analgesia were comparable between the sufentanil and tramadol groups. No patient in this study had a non-reassuring FHR tracing. The group of patients receiving tramadol had significantly longer-lasting analgesia. Five of the 20 patients receiving tramadol also presented with vomiting, which is the only major side effect noted with tramadol in this study.

5. INTRAVENOUS ANALGESIA

Neuraxial analgesia has become the ‘gold standard’ for obstetric analgesia. Unfortunately it cannot be used in all parturients, e.g. tendency towards bleeding, spinal deformities, spinal instrumentation, and patient refusal. In these cases alternatives need to be explored for pain relief.

Pethidine is most widely used for labour pain analgesia because of familiarity and low cost, although the efficacy of pethidine has been questioned. Pethidine has been shown to significantly affect FHR variability, accelerations and decelerations, during labour [38]. No significant differences in FHR changes were shown between pethidine and epidural analgesia [39].

Long *et al*. [40] studied tramadol patient controlled analgesia (PCA) compared to CSE with patient controlled epidural analgesia and a control group without analgesia for comparison of risks and benefits. CSE analgesia resulted in faster onset and better pain relief than PCA with tramadol. There were no differences in FHR and uterine contractions among the three groups. The authors concluded that PCA with tramadol is a useful alternative to CSE but may be accompanied by newborn depression as Apgar scores were lower in the tramadol group.

The reported analgesic properties of systemic opioids in labour are poor, but PCIA has proven to have phychological benefits, and when used with remifentanil allows for very rapid drug titration. [41].

The reported use of remifentanil for labour pain analgesia in the literature have described various methods of administration with inconsistent results. Mostly remifentanil is used in PCA setting, with or without a basal infusion. In one study by D’Onofrio *et al*. 205 parturients received a continuous infusion of remifentanil without PCA to examine analgesic effect, patient satisfaction and maternal and neonatal safety of this method of administration [42]. Infusion rates varied between 0.025 µg/kg/min – 0.15 µg/kg/min. Oxygen saturation remained above 95% at all times without oxygen supplementation. No changes in FHR variability score were detected, and during the 30 minute study period moderate analgesia was observed with good patient satisfaction.

PCA with remifentanil compared to epidural levobupivacaine with fentanyl was studied in a randomized controlled, double-blinded trial [43]. This study concluded that analgesia with epidural is superior, sedation was more common in the remifentanil group and the number of parturients with nausea was larger in the remifentanil group. The groups were not different in terms of abnormalities in FHR tracings.

However, discussion remains about safety and efficacy of PCA with remifentanil. Labour pain analgesia by remifentanil is modest and the risk for maternal sedation and oxygen desaturation even in the presence of oxygen supplementation remains [43]. On the other hand, PCA with pethidine has an even higher risk for oxygen de-

saturation [44]. Less FHR changes have been reported using PCA remifentanil as compared to PCA pethidine [44]. Hill [45] performed a retrospective analysis of 5410 consecutive deliveries. 28% PCA remifentanil, 22% epidural analgesia and 33% intramuscular pethidine analgesia with similar neonatal outcomes in all three groups. Van de Velde [46] on the other hand argues that remifentanil crosses the placenta readily and causes foetal immobility (during in utero surgery) and loss of foetal heart rate variability. He concludes that routine use of PCA with remifentanil cannot be promoted before extensive studies have been done to evaluate the effects of remifentanil on foetus and neonate [46].

6. ACUPUNCTURE AND ACUPRESSURE

As many women like to avoid invasive and/or pharmacological methods of pain relief during labour sometimes acupuncture is recommended. The evidence on acupuncture remains unclear. Acupuncture seems to have no detrimental effects on FHR. In one study there seemded to be a reduction of foetal baseline heart rate and more accelerations were observed during acupuncture [47]. In another study by the same group the foetal heart rate was reduced only by acupuncture and moxibustion combined [48].

In a study of moxibustion alone cardiotocograms were made 10 minutes before, 20 minutes during and 10 minutes after each session and there was no alteration or abnormality detected [49]. Cochrane review concludes that acupuncture and acupressure may have a role in reduction of pain during labour, but there is a need for further research [50].

7. AETIOLOGY OF FHR CHANGES

Several hypotheses have been proposed in the literature as to the origin of the FHR changes and foetal bradycardia observed with effective labour analgesia. In 1971 a comparison was made between FHR changes and pH of foetal blood. Decelerations and a loss of beat-to-beat variability appeared to be associated with foetal acidosis and therefore foetal asphyxia [51]. Huovinen *et al*. [6] found a higher incidence of FHR changes in the supine position when compared to lateral position. Preston *et al*. [52] reported a 15% incidence of severe FHR changes in parturients in supine wedged position compared to the left lateral position. These changes were attributed to occult aortocaval compression. This was contradicted by Eberle and co-workers [27] who found that prolonged decelerations were not related to maternal position, but 8 of the 11 episodes they noted were associated with uterine hyper tonus or tetany.

Segal and co-workers [53] used gravid rat uteri to show that epinephrine and norepinephrine have effects on uterine tone. Epinephrine caused dose dependent reductions in uterine activity. Norepinephrine alone increased uterine activity. Maternal epinephrine levels decline after effective labour analgesia but norepinephrine levels remain relatively unchanged.

Four years earlier Clarke *et al*. [22] proposed the following mechanism for foetal bradycardia following analgesia: Pain relief leads to a decrease in output of the sympathetic nervous system (effective labour analgesia leads to a decrease in circulating epinephrine levels). Epinephrine is a tocolytic. Decreasing epinephrine will cause an increase in uterine tone which will decrease placental blood flow. If placental blood flow is decreased enough there will be a subsequent foetal bradycardia.

Cascio *et al*. [54] also noted a reduction in maternal plasma epinephrine concentrations following both epidural and spinal analgesia, while plasma norepinephrine stayed the same or even increased slightly. They also observed faster decrease in plasma epinephrine in parturients who received spinal opioids when compared to epidural bupivacaine, which offers a possible explanation for the faster onset of FHR changes in CSE compared to epidural analgesia. The mechanism by which higher doses (fentanyl 25 µg - 50 µg [23,25], sufentanil 7.5 µg [31]) of intrathecal opioids more often lead to FHR changes remains unclear.

8. CLINICAL MANAGEMENT OF FOETAL HEART RATE ABNORMALITIES ASSOCIATED WITH LABOUR ANALGESIA

There are few data to determine the impact of epidural analgesia on pre-existing FHR abnormalities. Most studies exclude these patients. Fogel *et al*. [28] included 30 patients with FHR abnormalities pre-analgesia. In most cases these FHR abnormalities persisted.

Regardless of the aetiology of the FHR abnormalities, the key is managing these changes correctly when they occur. In all of the studies reviewed the incidence of FHR changes is relatively high, 3% - 20% [25,27,28], but this does not lead to higher incidence of caesarean section. Caesarean section is probably avoided by adequate treatment of these FHR changes. The use of uterine displacement and changing maternal position to relieve any aortocaval compression. Correcting any hypotension using phenylephrine in 50 µg - 100 µg increments (or ephedrine in 5 mg - 10 mg increments) and intravenous fluids. Giving extra oxygen. Stopping administration of oxytocin because of the association of FHR changes with uterine hyper stimulation. Administration of a tocolytic agent should be considered [20,55]. Uterine hyper tonus may be reversed by intravenous nitro-glycerine 60 µg - 90 µg, to be repeated when hyper tonus remains [56].

Nitro- glycerine reduces uterine contractility by raising intracellular cyclic Guanosine Monophosphate (cGMP) which in turn inactivates myosin light-chain kinase. One can also relax the uterus by terbutaline 0.25 mg i.v. but this causes a much longer relaxation of the uterus combined with maternal tachycardia because of action on beta-2-receptors. Activation of beta-2-receptors leads to inhibition of myosin light-chain kinase resulting in relaxation of the uterine muscle. Effective treatment of uterine hyper stimulation allows for normalisation of uterine and placental perfusion, and thus for normalisation of FHR tracings.

9. CONCLUSIONS

From the available literature we conclude that induction of labour analgesia can result in FHR changes and severe foetal bradycardia. Most likely this is due to uterine hyper tonus secondary to an acute drop in plasma levels of epinephrine. As higher doses of intrathecal opioids seem to be related to more frequent non-reassuring FHR tracings, administration of high doses of intrathecal opioids (≥7.5 mcg sufentanil) is best avoided.

Mechanisms of action for this high dose opioid effect are unknown. Many other factors may be related to FHR changes after labour analgesia. Further research on the different factors influencing FHR changes during labour analgesia is needed, as well as research directed at clarifying the specific mechanism of action of "high" doses of intrathecal opioids on FHR. Only then can prevention of FHR changes after labour analgesia be achieved.

When FHR changes occur it is of vital importance that the parturient is treated immediately. FHR changes are not an uncommon effect of effective labour analgesia but should not affect the outcome of the delivery or neonatal health.

10. COMPETING INTERESTS/FUNDING

The authors declare that they have no competing interests, and that there was no funding for this review article.

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