A41

Association of a Polymorphism of the Beta-2 Adrenergic Receptor with Pre-eclampsia

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Introduction Evidence suggesting that genetic factors are implicated in the genesis of pre-eclampsia (PE) are numerous (1). The regulation of vascular tone has been correlated with genotypic variability (2) and is determined in part by circulating vasoactive agents such as beta-2 adrenergic receptor agonists (β_2AR). It is possible that mutations of the β_2AR could contribute to the occurrence of PE. There are several genetic variants of the human β_2AR (1). At position 16, substitution of glycine (gly) for arginine (arg) results in increased down-regulation of the receptor, while substitution of glutamate (glu) for glutamine (gln) at position 27 leads to decreased down-regulation. Our hypothesis is that PE may be preferentially associated with a particular genotype of the β_2AR, which could be responsible for the altered basal vascular tone and vascular response to sympathetic stimulation occuring in PE.

Methods With IRB approval and informed consent, we collected blood samples from 52 Hispanic parturients with PE and compared it to 185 Hispanic controls [C] who delivered at term. PE was diagnosed when hypertension (systolic >140 and/or diastolic >90 mmHg) with proteinuria (>0.3g/24h) after 20 weeks of gestation were present, according to the ACOG 1996 definition. Genomic DNA was isolated and the alleles of the β_2AR were identified by established techniques (4). Data were analyzed using χ^2 tests.

Results The difference in the genotype distribution between PE and control subjects almost achieved statistical significance (p=0.053). The glu allele was negatively associated with PE (p=0.013).

Table: Genotype distribution

	Arg16Arg	Arg16Gly	Gly16gly	Gln27gln	Gln27glu	Glu27glu
PE (n=52)	35%	35%	30%	87%	9%	4%
C (n=185)	31%	41%	28%	70%	9%	21%

Discussion It is intriguing to note that the gln→glu mutation results in absent down regulation of the β_2AR, which would allow the sustained effect of β_2AR agonists. This association, if confirmed in a larger sample, might have implications for the risk factors and management of PE.

Refs: 1. Electrophoresis, 1997; 18, 1646-9. 2. Pharmacokinetics 1991;20:350-7. 3. J Allergy Clin Immunol 1999; 104:S42-6; 4. Pharmacogenetics 1999,9:511-6.

A42 (Poster 1)

A Comparison Of Intrathecal Fentanyl And Sufentanil For Labor Analgesia

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Introduction. The use of intrathecal (IT) opioids for labor analgesia continues to gain popularity, yet there are limited data to guide this use. Previously, we established an ED50 for 60 min of labor analgesia using both fentanyl[1] and sufentanil[2] (18μg and 4μg, respectively). The current study utilizes double these doses to approximate an ED95, and compares the duration of analgesia and side effects of IT fentanyl and sufentanil at this ED95 dose range.

Methods. Following IRB approval and written informed consent, fifty healthy nulliparous parturients were randomized to receive IT fentanyl 36μg, or sufentanil 8μg, via a CSE technique and by double blind design. Pain relief, side effects, block height, maternal vital signs, and fetal heart rate were assessed. The duration of spinal analgesia was considered to be the time from injection of study drug to the time of the patient's first request for additional analgesia, at which time the epidural catheter was dosed with lidocaine.

Results. The duration of spinal analgesia was significantly longer with IT sufentanil than with fentanyl (106.7 ± 30.7 min vs. 87.2 ± 29.7 min)(p<0.03). Sufentanil also caused significantly more subjective leg weakness than did fentanyl (60% vs. 28%; p<0.05), although motor block was absent in both groups. Other side effects, patient demographics, duration of labor, mode of delivery, pinprick sensory levels, VAS pain scores, and Apgar scores were similar between groups. (Data analyzed by Chi[2] and student's T-Test; P<0.05 significant).

Conclusion. Analgesia from sufentanil lasts longer than with fentanyl for early labor pain when 2x ED50 doses are compared. The longer duration may be as a result of inherent physiochemical properties of sufentanil, such as greater lipid solubility. However, it is also possible that the dose-response curves of fentanyl and sufentanil are not parallel, and therefore we have not chosen equipotent doses by doubling the ED50's. In conclusion, when using IT opioids alone for early labor analgesia, sufentanil 8μg can be expected to last 20 min longer than fentanyl 36μg, with a minimal increase in side effects. One must keep in mind, however, that sufentanil costs much more than fentanyl, and it is more difficult to prepare exact doses due to its high potency-to-concentration ratio.

References.
1. Anesthesiology 1998; 89: A1069
2. Anesthesiology 1999; 91:1293-8

A43 (Poster 2)

Cost efficiency of PCEA versus single dose intrathecal morphine for analgesia after cesarean section.

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Aim of the study. To evaluate the quality of analgesia and costs between PCEA and a single bolus of intrathecal morphine (1) during the first and second day after C-section.

Methods. After approval by the ethics committee and informed consent , 40 patients undergoing C-section under CSE- anesthesia were randomly assigned to receive a single intrathecal dose of morphine 0.15mg or a PCEA device delivering bupivacaine 2.4mg (0.06%) with sufentanil 4μg (lock-out time 10 min.). During 48 hrs VAS pain scores (rest and dynamic) , side-effects and additional medication were registered every 6 hrs. Rescue medication consisted of propacetamol 2g with/without tramadol 100mg. Costs were calculated including staff and/or nurse interventions , equipment , pain and additional medication.

Results. There were no demographic differences between both groups. VAS scores at rest were significantly better in the PCEA group from 24 till 48 hours after delivery whereas dynamic pain scores were better with morphine at 6 hours but again became better in the PCEA group from 24 till 42 hrs. Morphine caused significantly more nausea and vomiting than PCEA (p<0.05). No differences were noticed with respect to pruritus , sedation and urinary retention. At 12 hrs more PCEA treated patients had sensory deficit and motor impairment (≤Bromage 1 score) but during the subsequent hours this gradually disappeared. Neither quality of sleep or overall satisfaction differed between the two groups. The overall costs totalled an amount of 72,2 ± 18.11Euro (1 Euro = ±1.02 USD) whereas for morphine this reached 36.30 ± 27.6 Euro (p<0.01).

Conclusion. PCEA with sufentanil-bupivacaine provides better pain relief after C-section at a reasonable extra cost and with less side-effects than a single intrathecal morphine bolus.

References. 1. Dahl et al. Anesthesiology 1999 ; 91 : 1919-27.

A44 (Poster 3)

Combined Spinal Epidural vs. Epidural Analgesia: Part 1: Anesthetic Outcome

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Introduction: Nonrandomized studies suggest that the needle through needle combined spinal epidural (CSE) technique is associated with a decreased risk of accidental dural puncture,[1] and an increased probability of a working epidural catheter.[2] Inability to obtain CSF and headache are possible limitations of CSE.

Methods: This protocol was approved by our Human Studies Committee. A random number generator assigned either CSE or epidural analgesia to each day between August 1, 1997 and January 11, 1998. Parturients consenting to the study received that day's randomly determined analgesic technique. Neither the patient nor her obstetrician was aware of the assigned technique. Labor analgesia was induced and maintained according to a specific protocol (table 1).

Table 1: Protocol for induction and maintenance of labor analgesia

Technique	Induction-early labor	Induction-advanced labor	Maintenance
CSE	10 μg intrathecal (IT) sufentanil	10 μg IT sufentanil + 2.5 mg IT bupivacaine	0.083% bupivacaine+
Epidural	10 mL 0.125% bupivacaine+10 μg sufentanil	15-20 mL 0.125% bupivacaine + 10 μg sufentanil	0.33 μg/mL sufentanil at 12 mL/hr

Results: Thirty six (0.07%) women assigned to the CSE group received epidural analgesia because of inability to obtain CSF (n = 29), paresthesia (n = 3), or both (n = 3). Other pertinent results are shown in Table 2.

Table 2: Effect of technique on efficacy and complications [% (95% CI)]

	Failed Block	Accidental Dural Puncture	Headache	Blood Patch
CSE	0.8%	0.8%	4.1%	0.4%
(n = 495)	(0% – 1.6%)	(0% – 1.6%)	(2.2% - 6.0%)	(0% –1.0%)
Epidural	0.9%	1.0%	8.3%	0.6%
(n = 511)	(0.1% - 1.8%)	(0.1 %– 1.8%)	(5.9% – 10.8%)	(0% – 1.2%)

Discussion: Previous, nonrandomized trials have reported some slight advantages associated with the CSE technique.[1,2] Our data suggest that both techniques can be used to safely and reliably to relieve labor pain.

References: 1. Norris MC, et al. Anesth Analg 1994;79:529. 2. Norris MC. Int J Obstet Anesth. 2000:In Press.