TITLE : EFFECT OF EPIDURAL CLONIDINE ON EPIDURAL FENTANYL ANALGESIA AND PHARMACOKINETICS IN POSTOPERATIVE PATIENTS.

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Epidural clonidine prolongs the analgesic effect of epidural opiates (1). Clonidine might act via α2 receptors of the dorsal horn of the spinal cord (2). Since clonidine induced an α2 mediated vasoconstriction (3), it might also impair the plasma resorption of epidural opiates. This study was designed to assess this effect.

18 ASA II-III postoperative patients were included in this study after informed consent and ethical committee approval. 24 H following abdominal surgery, conducted under epidural plus general anesthesia without opiates, the patients were assigned randomly in 2 groups to receive either epidural fentanyl 100 mcg diluted in 10 ml of isotonic saline solution or fentanyl 100mcg plus clonidine 150 mcg in the same solution. Continuous monitoring included heart rate, blood pressure and arterial oxygen saturation. Pain was assessed on a visual analogue scale (VAS), (0 ->10), before and every 15 min during one hour following the epidural injection and then every 30 min during 11 hours. When VAS score was >5, the patients received IV paracetamol. Pain relief (%) was calculated as: $\frac{\text{initial VAS score-VAS score}}{\text{initial VAS score}} \times 100$.

Duration of analgesia was the time elapsed between the epidural injection and the paracetamol administration. Plasma fentanyl concentrations were determined by a radioimmunoassay from arterial blood samples withdrawn before 5, 10, 15, 20, 25, 30, 40, 60, 90, 120, 180 , 240 , 300 and 360 min after the epidural injection. Statistical analysis used ANOVA for repeated measurements, paired and unpaired t test; values are expressed as mean±SD.

Demographic data were comparable in the 2 groups. Epidural clonidine significantly prolonged the analgesic effect of epidural fentanyl (table 1). A more important decrease in systolic arterial pressure was noticed in the clonidine group (maximum decrease 35.5±13.3% vs 15.5±17.9%). Fentanyl plasma kinetics were comparable in the two groups (table 2).

Table 1: **Pain Assessment**

	initial VAS score (0-10)	max pain sedation (%)	analgesia duration (min)
fentanyl	6.0±1.0	97±10	250±64
fentanyl+ clonidine	6.1±1.2	84±22	543±183*

*p<.05, intergroup comparison.

Table 2: **Epidural Fentanyl Kinetics.**

	Cmax (rg.ml-1)	Tmax (min)	AUC (0-180min) (rg.ml^{-1}.min)
Fentanyl	.32±.16	87±94	40.5±26.0
Fentanyl +Clonidine	.31±.10	87±119	30.2±14.2

Cmax: peak plasma fentanyl concentration ; Tmax: time to reach Cmax ; AUC (0-180min) : Area under curve from 0 to 180 min

This study confirms that the addition of clonidine to epidural fentanyl increases the duration of analgesia. Since clonidine failed to significantly impair fentanyl kinetics, these results rule out the hypothesis that epidural veins vasoconstriction may contribute to the effect of epidural clonidine.

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TITLE: **EPIDURAL FENTANYL BY PCA AND CONTINUOUS ADMINISTRATION**

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Epidural administration of morphine and pethidine by patient controlled analgesia (PCA) is an effective method of post-operative pain relief (1). Epidural fentanyl analgesia by PCA and continuous infusion have both been reported (2, 3). However, no comparative study on these two methods is available. Therefore the aim of our study was to compare continuous and PCA administration of epidural fentanyl.

The study was approved by the Ethical Committee and informed consent was obtained. Thirteen ASA 1 or 2 patients, aged 18 to 75 yrs, underwent laparotomy with a midline incision under general anesthesia followed by a continuous epidural infusion of bupivacaine 0.1% (0.1mg.kg $^{-1}$.h^{-1}) combined to fentanyl. Epidural fentanyl administration was randomly performed either by continuous infusion (n = 7, 1 μg.kg^{-1}.h^{-1}) or by PCA (n = 6, bolus of 15 μg,lock up time of 12 min). Visual analogue pain score (0-100), verbal pain score (0-3), sedation score (0-4), respiratory rate and O2 saturation were measured at 1, 2, 4, 8, 12, 16, 20 and 24h. Blood gas analysis was performed at 4, 12, 18 and 24h. Side effects (pruritis, nausea, respiratory depression) were noted. For statistical analysis beetween groups, ANOVA with repeated measures and Student's t test were used. P<0.05 was considered significant.Values are given as the mean ± S.D..

The two groups of patients were comparable with respect to age, sex ratio, weight, height and duration of surgery. Analgesia (figure 1) and sedation scores, respiratory rate, SaO2 and paCO2 were similar in the two groups.The dose of fentanyl was significantly lower in the PCA group than in the continuous infusion group during 24h (425 ± 109 vs 1580 ± 258 μg 24h^{-1}, p<0.01) and for each 4h interval (figure 2). No respiratory depression was clinically detected.

Since side effects of epidural opioids are dose-dependant, the lower dose of fentanyl during PCA administration offers an advantage. In conclusion epidural PCA fentanyl when combined to a continuous bupivacaine administration, provides an efficient postoperative analgesia with smaller doses of fentanyl than continuous epidural infusion.

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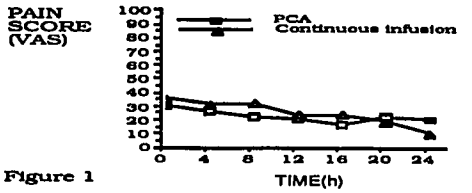

Figure 1

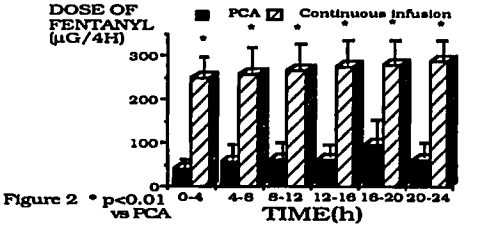

Figure 2