Title : ADDITIVE EFFECTS OF ORAL CLONIDINE AND FENTANYL ON ISOFLURANE-INDUCED HYPOTENSION : A DOUBLE-BLIND RANDOMIZED STUDY

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Introduction. Clonidine (C) has been shown to reduce fluorinated volatile agent requirements and narcotic doses.[1,2] C is able to facilitate deliberate hypotension during anesthesia.[3,4] In these studies, an important concern is the absence of double-blind experimental protocols. In this context, the possibility of investigational bias and drug interactions cannot be overlooked. The aim of this double-blind randomized study was to assess the respective roles of oral C pretreatment and fentanyl (F) and their combination during isoflurane-induced hypotension on hemodynamic changes and anesthetic requirements.

Methods. The protocol was approved by our Human Investigation Committee. Twenty-eight ASA I-II patients (mean age 56.7 years, range 36-79) undergoing total hip replacement gave their consent. They were randomly assigned to 4 groups (n=7) according to C pretreatment (C^+) or its placebo (C^-), F anesthesia (F^+) or its placebo (F^-). C^+ (3.5 $\mu g.kg^{-1}$) in groups C^+F^+ and C^+F^- and C^- in groups C^-F^+ and C^-F^- were administered first the evening before surgery, and then with diazepam (0.3 $mg.kg^{-1}$) premedication 2 hours before surgery. No vagolytic medication was given. Anesthesia was induced with thiopental (5 $mg.kg^{-1}$), pancuronium (0.1$mg.kg^{-1}$) and lidocaine (1.5 $mg.kg^{-1}$). A continuous F^+ infusion in groups C^+F^+ and C^-F^+ or F^- in groups C^+F^- and C^-F^- was started at a rate of 3 $\mu g.kg^{-1}.h^{-1}$, after a loading dose of 3 $\mu g.kg^{-1}$. After intubation, patients were ventilated with an O_2/ N_2O mixture (FiO_2 = 0.5) to which isoflurane (Iso) was then added. Monitoring consisted of a 7.5 Fr Swan Ganz catheter placed under local anesthesia on the evening prior to surgery, ECG, radial artery cannula, and fluorinated volatile infrared analyzer. Hemodynamic measurements were performed at 4 time periods : before pretreatment (T0), in premedicated patients before induction (T1), 20 min after starting Iso end-tidal concentration (ET) = 0.6% (T2) and 20 min after stable hypotension (MAP = 55 mmHg) (T3). Data were compared by ANOVA at each time period of the study; $p<0.05$ was considered as significant.

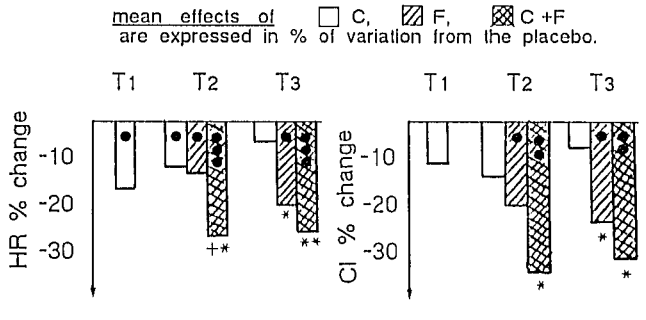
Results. Demographic and basal vital signs were not different between groups. There were no significant interactions between C and F with respect to hemodynamic data at each time period and Iso ET requirement for maintaining hypotension. Their effects were additive. In C^-F^+ and C^+F^- groups, hypotension was easy to obtain, but C alone was unable to reduce the Iso requirement significantly (table). During the study, SI and SVRI were not significantly different between groups. At T1, MAP was lower ($p<0.05$) with C^+ than with C^-. At T2 MAP did not differ between C^+ and C^- and between F and C, but was significantly lower ($p<0.05$) with F^+ than with F^-. CI and MAP are shown in the figures.

Table: *p<0.05, ** p<0.02 vs C^-F^-, (°) p<0.05 vs C^+F^+

group	C^-F^-	C^-F^+	C^+F^-	C^+F^+
Iso ET% mean±SD	2.13 ±0.41	1.60* ±0.65	1.8(°) ±0.60	1.25** ±0.40

Discussion. C and F have a central effect decreasing sympathetic outflow and increasing vagal tone.[4,5] During Iso-induced hypotension, HR and CI were not significantly different with C than with the placebo, whereas for the same level of hypotension F led significantly to a lower HR and CI than placebo or C did. These effects are not likely to be competitive but additive when F is associated with C pretreatment. It is suggested that the mechanisms accounting for inhibition of baroreflex sensitivity were different. With sedative, analgesic and moderate hemodynamic effects, C could be a safe alternative to narcotic analgesia. But the hemodynamic additive effects of C and F (bradycardia and fall in CI) could limit the practical use of adding C to the narcotic anesthetic technique.

FIGURES (N=28)



vs placebo • p<0.05, •• p<0.02, •••p<0.01
vs F + p<0.05, ++ p<0.02, vs C * p<0.05, ** p<0.02

References
1. Ghignone M. *Anesthesiology* 67 :3A, A38 1987
2. Flacke J W. *Anesthesiology* 67 : 11-19, 1987
3. Ghignone M. *Anesthesiology* 67 : A38, 1987
4. Woodcock TE. *Br. J. Anaesth* 60 : 388-394 1988.
5. Loubie M. In: Hypertension and Brain Mechanisms, *De Jongh ed* , 337-348, Elsevier, 1977