Summary of the results from the study “Suun limakalvolle annosteltu fentanyyli luuydinaspiraatioon ja -biopsiaan liittyvän kivun hoidossa” (EudraCT-number 2010-021811- 17)

Aim of the study: This randomized placebo-controlled study compared the pain-relieving effect of sublingual fentanyl with placebo during bone marrow aspiration and/or biopsy (BMAB).

Patients and methods: Adult patients having suspected or diagnosed haematological malignancy undergoing BMAB in Helsinki and Uusimaa district’s Meilahti hospital haematology outpatient clinic were considered for recruitment. Predetermined exclusion criteria were allergy to lidocaine or to the study drug, body mass index over 32 kg/m^2, unstable coronary artery disease, drug abuse or ongoing opioid replacement therapy and inability to communicate in Finnish or Swedish. Patients that were planning to drive a motor vehicle or going to work after the BMAB, having no competent escort or taking part to another clinical trial, were excluded as well.

After giving informed consent the eligible patients were thoroughly interviewed before randomization. Very anxious patients were allowed to receive additional anxiolytic medication (5-10 mg oral diazepam prescribed by the haematologist performing the BMAB).

160 patients were randomized to have either sublingual fentanyl (Abstral, ProStrakan Ltd, Galashiels, Scotland, UK) or placebo 10-30 minutes before the estimated start of the procedure. The randomization was performed with sealed envelopes. In the fentanyl group (80 patients), the fentanyl dosage was 200 ug but for patients over 70 years old, weighing less than 50 kg or having severe systemic disease, the fentanyl dose was 100 ug. The placebo group (80 patients) received a similar rapidly dissolving tablet without any pharmacologically active ingredients. The patient, the study nurse performing the interviews and the haematologist performing the BMAB were blinded.

All patients received a standardized local infiltration anaesthesia with lidocaine. Additional pain medication with intramuscular alfentanil was allowed if the analgesia was not considered appropriate. Blinded study nurse recorded the pain scores during various phases of the procedure. The level of sedation, peripheral oxygen saturation and non-invasive blood pressure were monitored during the procedure and 1 hour follow up period after the BMAB. After the procedure, patients rested in bed for the 1 hour follow up period and all side-effects were recorded.

The primary outcome of the study was pain in NRS (Numeral Rating Scale, 0-10) during various phases of the procedure. The study sample was planned based on a power analysis. Ordinal regression analysis was performed to analyze the primary outcome in the study groups. Logistic regression analysis was useed to compare side-effects between study groups. The statistical analyses were performed with SPSS version 17.0 (Chicago, IL, USA).

The hospital ethics committee approved the study protocol before the start of the trial (Helsinki Uusimaa Health District, diary number HUS 222/13/03/01/ 10) and the Finnish Medicines Agency Fimea was notified of the trial. The ethical principles of Helsinki declaration were followed during every step of the clinical trial.

Main results: The study period was from January 2011 to January 2012, when the last patient was recruited.

There were no statistically significant differences in the pain scores between patients receiving sublingual fentanyl or placebo. Median pain score during local infiltration anaesthesia in patients having received 100 ug sublingual fentanyl was 2 (range 0-8), 3 (range 0-8) in patients receiving 200 ug sublingual fentanyl and 3 (range 0-9) for placebo group. During bone marrow aspiration, the scores were 5 (0-9), 4 (0-10) and 4 (0-19) and for biopsy, 5,5 (0-8), 6 (0-9) and 4 (1-10), respectively.

There were no serious side-effects in the fentanyl group. Patients receiving sublingual fentanyl suffered from dizziness more often than patients receiving placebo ($P < 0.0001$, OR 7.24, 95% CI [2.69; 19.46]). Nevertheless, fentanyl did not cause excessive sedation and no significant drops occurred in the peripheral oxygen saturation or blood pressure values.

Conclusion: Sublingual fentanyl was not feasible in preventing pain during BMAB. Dizziness was more frequent in the fentanyl group than in the placebo group.

The results were published in the following research article containing in depth analysis of the results:

Kuivalainen AM, Ebeling F, Rosenberg PH. Premedication with sublingual fentanyl did not relieve pain associated with bone marrow aspiration and biopsy – a randomized feasibility trial. European Journal of Pain 2013; 17: 1357-64.