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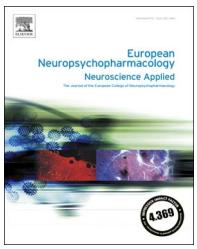

Delayed increase of thrombocyte levels after a single sub-anesthetic dose of ketamine – A randomized trial ☆

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Abstract
Recently, ketamine has been investigated as a potential antidepressant option for treatment resistant depression. Unlike traditional drugs, it yields immediate effects, most likely via increased glutamatergic transmission and synaptic plasticity. However, ketamine administration in humans is systemic and its long-term impact on blood parameters has not yet been described

☆Trial name: Ketamine in treatment resistant major depression (TRD) URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-023414-31/DE/ EudraCT number: 2010-023414-31.

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in clinical studies. Here we investigated potential sustained effects of ketamine administration *(0.5 mg/kg ketamine racemate)* on hematological and biochemical values in plasma and serum in a randomized double-blinded study. 80 healthy young participants were included and whole blood samples were collected 5 days before, and 14 days after the infusion. To assess the group effect, repeated measure analyses of co-variance (rmANCOVA) were conducted for the following blood parameters: levels of sodium, potassium, calcium, hemoglobin and number of erythrocytes, lymphocytes, and thrombocytes. RmANCOVA revealed a significant time by treatment effect on thrombocyte levels ($F_{1,\ 74} = 13.54$, $p < 0.001$, eta = 0.155), driven by an increase in the ketamine group (paired *t*-test, $t = -3.51$, df = 38, $p = 0.001$). Specificity of thrombocyte effect was confirmed by logistic regression, and in addition, no other coagulation parameters showed significant interaction. Moreover, the relative increase in the ketamine group was stable across sexes and not predicted by age, BMI, smoking, alcohol or drug use, and contraception. Our results describe aftereffects of sub-anesthetic ketamine administration on blood coagulation parameters, which should be considered especially when targeting psychiatric populations with relevant clinical comorbidities.

1. Introduction

Over the last ten years, there has been a surge in ketamine research as a potential antidepressant option for treatment resistant patients (aan het Rot et al., 2010; Walter et al., 2014; Zarate and Machado-Vieira, 2017). Rapid and efficient in alleviating depressive symptoms after a single *sub-anesthetic* dose, ketamine is considered in clinical situations where antidepressant treatment targeting serotonin or norepinephrine pathways does not show improvement or does not have an expected lag to clinical improvement such as for acute suicidality (Walter et al., 2014). *In medical and veterinary practice, ketamine has been used as an anesthetic, a post-operative analgesic, or in chronic pain diseases* (Elia and Tramèr, 2005). Administration of ketamine is systemic and it affects not only targeted neuronal systems but also the periphery.

Ketamine is metabolized by N-demethylation by liver microsomal cytochrome P450. Two isomers of ketamine exist: S(+) and R(-) ketamine, which differ in their pharmacological profile. S(+) has a four times higher affinity for NMDA receptors but lower behavioral side effects (White et al., 1985). Rates of demethylation and clearance of S(+) isomer are also larger than for R(-) or the racemate (Kharasch and Labroo, 1992). The major enzyme responsible for ketamine N-demethylation is the CYP3A4 isoform, while CYP2C9 and CYP2B6 have minor roles in its metabolic pathway (Dinis-Oliveira, 2017; Hijazi and Boulieu, 2002).

Next to clinical potential, *higher dose* ketamine is also taken as a recreational drug, and abuse can lead to cortical changes (Liao et al., 2011; Wang et al., 2013), cognitive decline and lower well-being (Morgan et al., 2010), and renal and urinary tract problems (Chu et al., 2008; Selby et al., 2008). Further, a case study of ketamine abusers reported changes in hematological parameters (Ng et al., 2010). Latter findings from addiction research argue for a better characterization of physiological and neural parameters for safe administration, especially in the case of repeated exposure as antidepressant medication (Sanacora and Schatzberg, 2015).

Thus far, attention in antidepressant ketamine trials has been given mainly to *acute side-effects such as* blood pressure *changes* (Liebe et al., 2017), *dissociative symptoms* (Luckenbaugh et al., 2014) and depression related biomarkers measured in blood, *i.e.* BDNF (Haile et al., 2014) during and after ketamine administration. Safety risks associated with other biomarkers such as coagulation status and cell count necessitate thus further inspection. Investigations in non-human primates have indeed shown changes in hematological properties after ketamine application: an acute drop in leukocyte and thrombocyte number immediately after infusion (Rovirosa-Hernández et al., 2011; Ündar et al., 2004), but an increase in thrombocytes after repeated anesthesia with ketamine (Lugo-Roman et al., 2010). Furthermore, ketamine analogues were suggested as a possible treatment option for thrombocytopenia (Kogan and Somers, 1993).

Therefore, in the present study, we investigated potential aftereffects on blood parameters used in clinical routine in a randomized, double-blind design. Hematology parameters, hemoglobin, and number of leukocytes, thrombocytes, and erythrocytes, and levels of sodium, calcium, and potassium were determined during safety laboratory, 1-20 days before and at the end of the trial, 10-20 days after the single sub-anesthetic infusion of ketamine or saline. Safety laboratory parameters were measured as a secondary outcome, as the primary goal was to assess neuronal changes in the glutamatergic system measured via magnetic resonance spectroscopy (Li et al., 2016). We did not have a strong hypothesis of the specific outcomes of a single parameter since it was not reported in previous clinical trials. Given positive reports on changes in *e.g.* BDNF levels, an increase in platelet counts was plausible given that thrombocytes are major pools of peripheral BNDF (Chacón-Fernández et al., 2016). In our trial, we hence assessed potential changes in coagulation status also in context of other safety markers. To contribute to future clinical integration of our findings, in a large set of healthy individuals, we controlled potential aftereffects for sex specificity and prediction by other

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