

# Comparison of Serum Cortisol during Elective Surgery, Acute Trauma and Sepsis to 'Stress Dose' Hydrocortisone Administration in Patients with Adrenal Insufficiency

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## Background

Patients with adrenal insufficiency require increased hydrocortisone replacement doses during surgery, trauma and infection to avoid life-threatening adrenal crisis. However, currently administered hydrocortisone doses are chosen empirically rather than on rational grounds, with huge variability in administration modes, total dose and dosing intervals. Here we investigated cortisol levels during stress situations in non AI patients compared to currently used stress dose hydrocortisone in patients with adrenal insufficiency (AI)

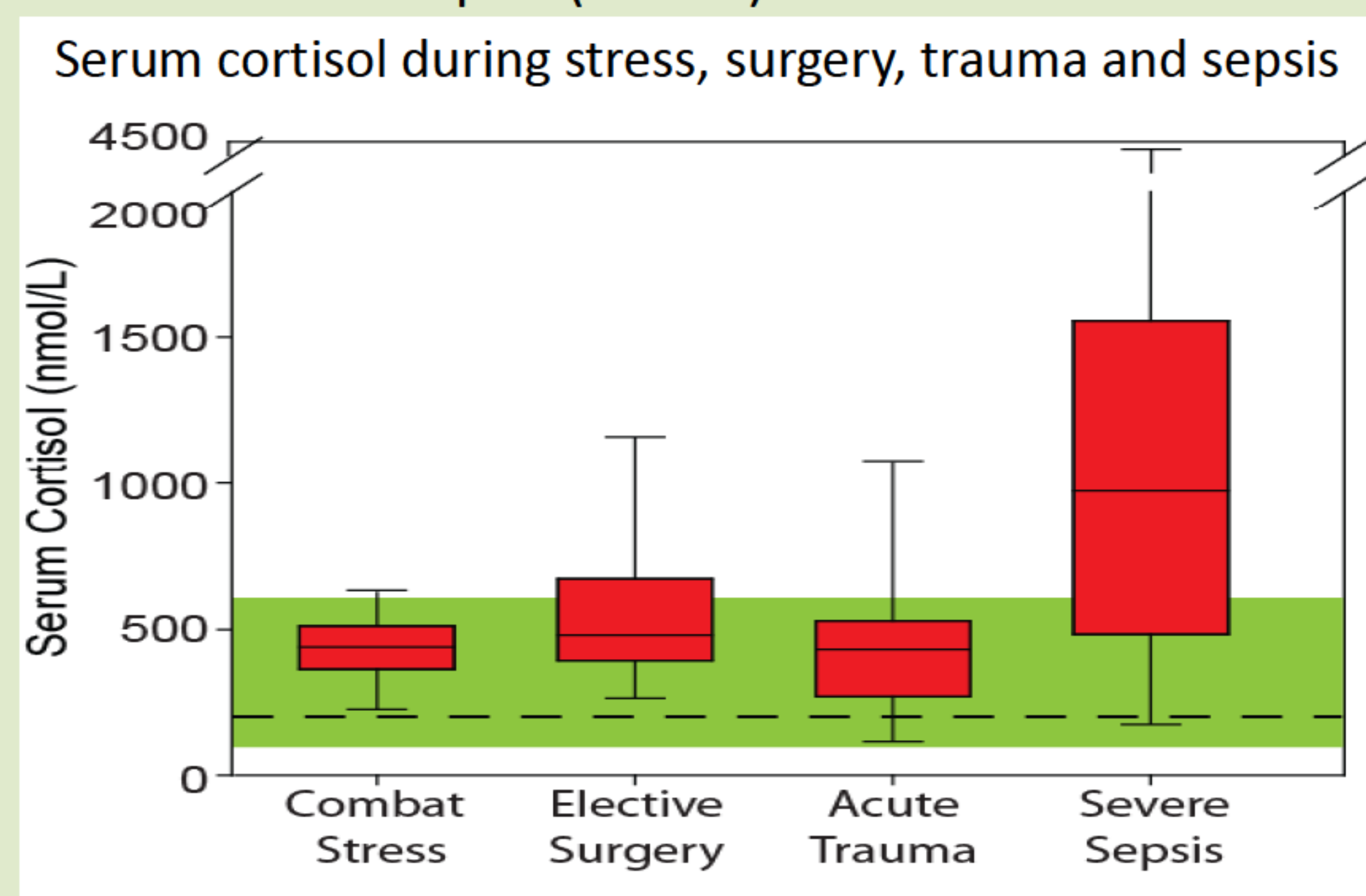
## Methods

Serum cortisol levels were quantified by liquid chromatography/tandem mass spectrometry (LC-MS/MS) on a Waters Xevo mass spectrometer with an Acquity uPLC chromatography system.

## Serum Cortisol during Stress

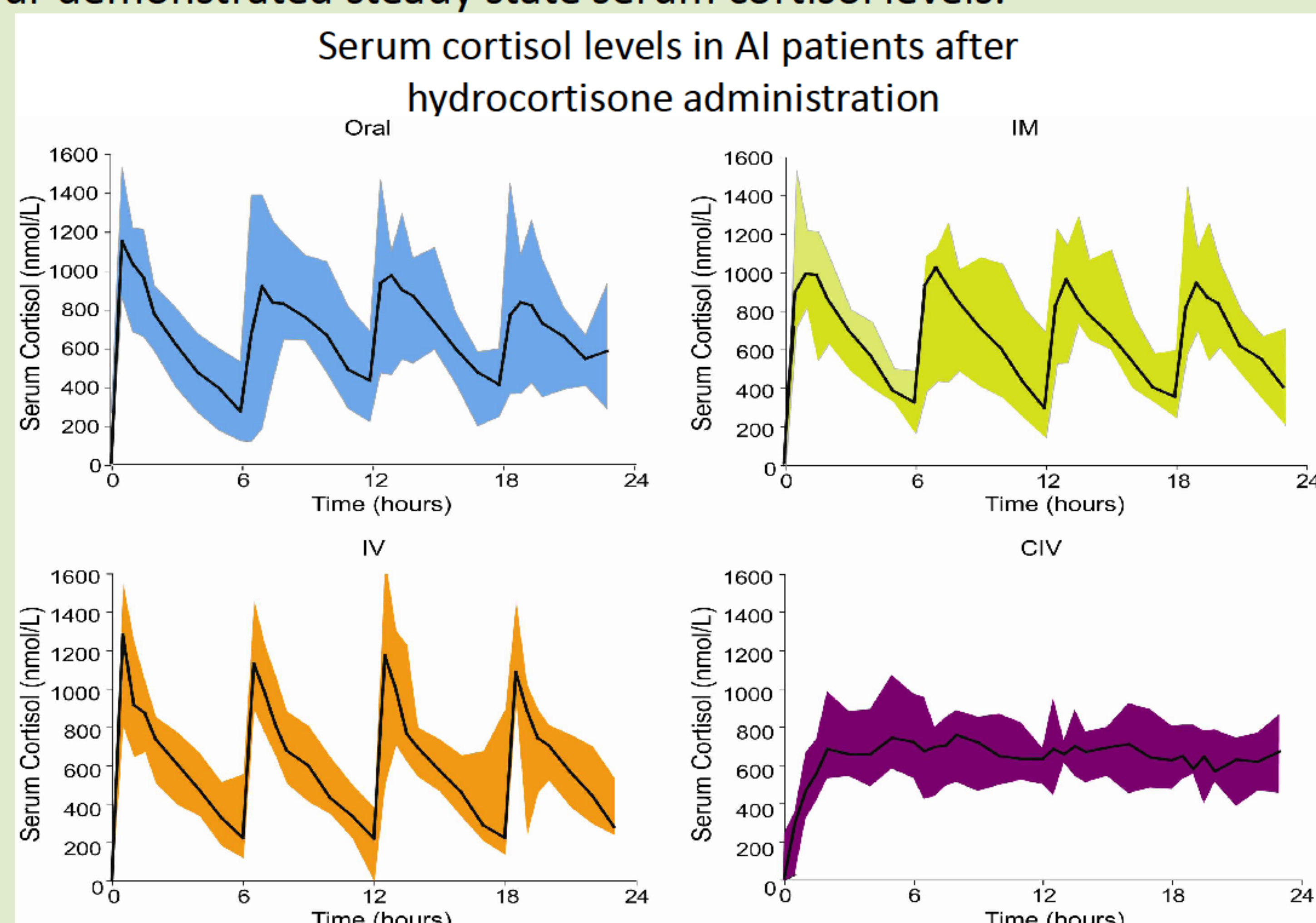
Firstly we determined median serum cortisol levels (5<sup>th</sup>-95<sup>th</sup>) observed in;

1. Healthy controls (n=86)
2. Soldiers under combat stress (n=105)
3. Patients undergoing elective surgery with general anaesthesia (n=22)
4. Patients after acute trauma (n=85)
5. Patients with severe sepsis (n=100)

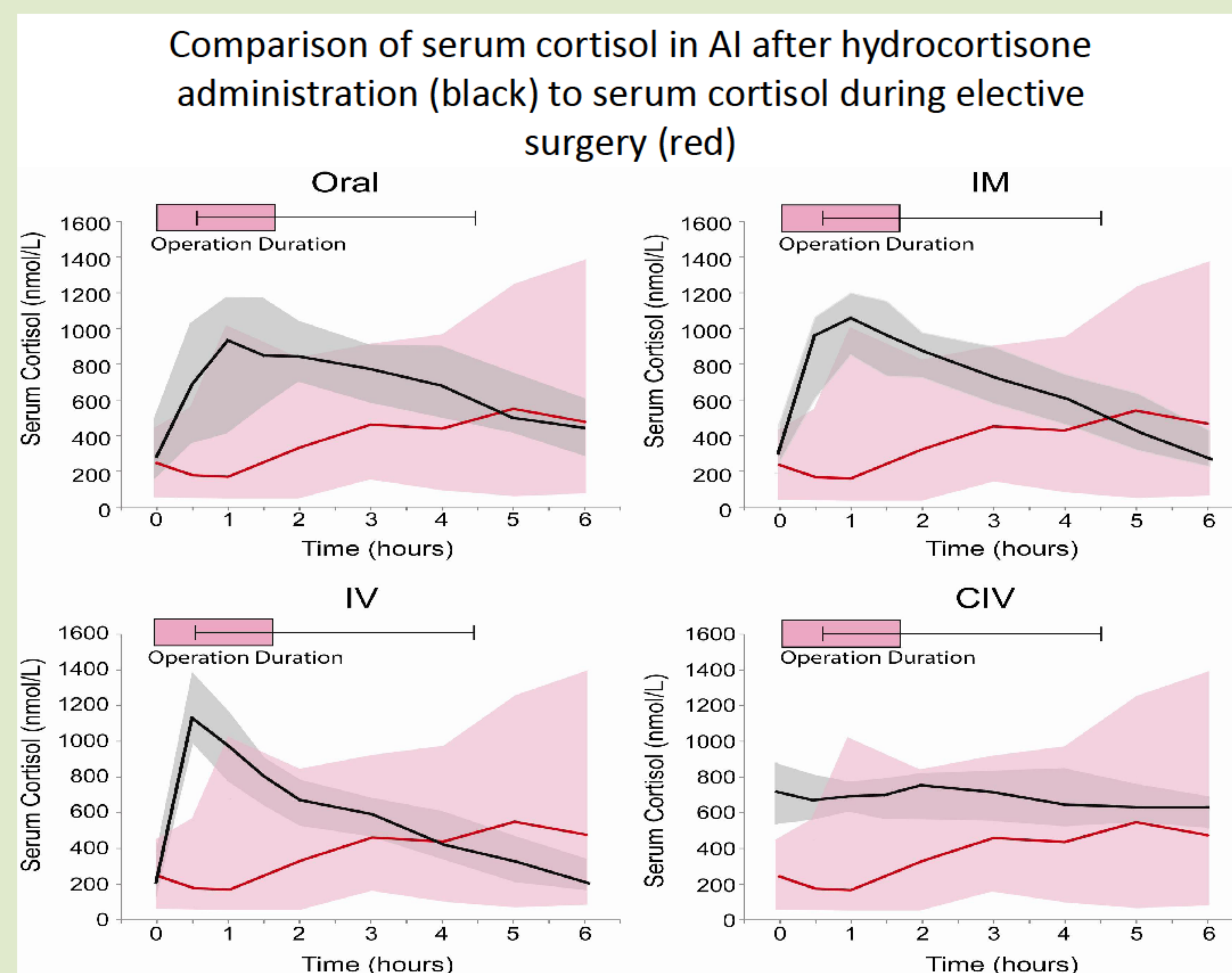


## Serum Cortisol After Hydrocortisone Administration in Adrenal Insufficiency Patients

Secondly, we undertook frequent sampling over a period of 24 hours in ten patients with primary adrenal insufficiency who received hydrocortisone 200mg/24h in four different administration modes: 50mg every 6 hours orally (O) or per intramuscular (IM) or intravenous (IV) bolus injection or 200mg/24h as continuous intravenous infusion (IV-C). Serum cortisol was observed to peak 0.5-1hr after hydrocortisone administration by O, IM or IV which decreased until the next dose. IV-C after the first hour demonstrated steady state serum cortisol levels.



## Comparison of Serum Cortisol in Elective Surgery to Hydrocortisone replacement in AI Patients



Initial cortisol peak concentrations after hydrocortisone in AI patients (black) exceeded surgical control levels (red), but decreased to less than the median several hours before repeat administration of O, IV and IM bolus.

By contrast, hydrocortisone via IV-C maintained steady state cortisol levels above the median of elective surgical controls throughout. Therefore **continuous IV rather than bolus administration** of hydrocortisone will avoid dangerous intermittent trough levels

## Optimal Dosage

Linear pharmacokinetic modelling combined with mixed effects regression calculated **the optimal dose and administration mode** for patients with adrenal insufficiency exposed to pathological stress due to trauma, sepsis or surgery is **an initial bolus of 50-100mg hydrocortisone IV, followed by continuous IV infusion of 200mg/24h.**

