

Using the BIS Monitor to Determine the Time for Peak Onset of Sedation

Christopher Heard; Kristen Heard; Julia Kollesar; Julie Heard; Ravi Piryani; Jonathan Malinovsky.

Department of Anesthesiology, University @ Buffalo.

INTRODUCTION

Pharmacokinetic models are used to predict plasma drug concentrations, which are considered to be equivalent to the sedative agent’s concentration effect in the brain. More recently, a new concept of effect site concentration (1) is now considered to be a better model. This takes into account drug entry and drug action delay effect (due to receptor interactions, enzymatic effects, and membrane transport etc). The constant, Ke0, which is used to calculate the effect site concentration, can be calculated theoretically using complex mathematics or more simply by measuring the time to peak clinical effect from a sedation bolus. The BIS monitor is a multi-processed EEG that displays the depth of hypnosis, the clinical effect of sedative agent, as a number 1-100 (deep coma to awake). This should enable the assessment of not only the peak effect, but for this study, the time required to achieve this (2).

The aim of this study was to estimate the time to peak effect in children for boluses of Midazolam and Fentanyl and Propofol using the BIS monitor to determine the depth and time to peak effect.

METHODS

Two age groups of children are used (G1: 11 to 14 years old and G2: 15-17 years old). All were children who are undergoing a dental procedure under deep propofol infusion sedation. Exclusion criteria included: complex medical history, recreational drug use, use of multiple psychotropic medications or ADHD medications and BMI > 25. The BIS monitor and the sedation monitor were time synchronized. The patient’s forehead was cleaned with an alcohol wipe and the BIS probe applied. The BIS monitor downloaded the real-time BIS data to a PC via a serial cable, into an Excel readable file. After baseline BIS recording, a bolus of the study sedative agent (Midazolam, Fentanyl or Propofol) was given followed by a 10 mL NS flush. All three agents are part of our age/weight based standardized deep sedation regimen. The BIS monitor was then observed during the sedation onset. The time of the initial study dose and the initial sedative effect felt by the patient was recorded.

Once the study sedation drug bolus had resulted in its BIS nadir (peak effect), the sedation was continued as planned using additional midazolam and / or fentanyl as needed and a propofol infusion.

Table 1. DEMOGRAPHICS

GROUPS	NO.	AGE (YRS)	WEIGHT (KG)	BMI	DOSE WT (KG)	ASA
M G1	12	13.1	58.3	21.0	53.9	1.3
M G2	12	16.2	70.2	22.9	66.5	1.4
F G2	12	16.2	63.0	21.8	60.8	1.4

Table 2. STUDY SEDATION DOSING

GROUPS	BOLUS/START MID MG	TOTAL MID MG	BOLUS/START FENT MCG	TOTAL FENT MCG	TOTAL MID MG/KG	TOTAL FENT MCG/KG
M G1	3.8	4.0	45.8	95.8	0.069	1.64
M G2	4.0	5.3	50.0	100.0	0.058	1.46
F G2	2.0	4.3	93.8	97.9	0.033	1.59

Table 3. TIMING (MINUTES)

GROUPS	SED TIME	PROC TIME	PHASE 1	PHASE 2	DC TIME
M G1	8.4	13.6	22.4	16.1	38.5
M G2	8.6	19.8	19.1	12.4	31.5
F G2	8.5	14.6	18.5	15.8	34.3

Table 4. INITIAL CLINICAL ONSET AND PEAK EFFECT

GROUPS	AVERAGE DOSE BIS	AVERAGE INITIAL EFFECT BIS	AVERAGE PEAK EFFECT BIS	Ave. TIME TO PEAK EFFECT (S)
M G1	94.5	86.4	70.9	120
M G2	94.2	87.5	76.7	125
F G2	94.2	93.9	89.1	96

Table 5. PEAK EFFECT RESPONSE **p=0.028 1W ANOVA*

GROUPS	BASELINE BIS (1 MIN PRE)	ONSET_BIS	% SIG from BASELINE
M G1	93.6	84.3	91.7
M G2	94.4	85.6	91.7
F G2	95.1	94.6*	16.7

REFERENCES

1. JR. Sneyd, A. E. Rigby-Jones. Effect site: who needs it? British Journal of Anaesthesia 98 (6): 701 - 4 (2007).
2. Munoz HR, Leo PJ et al. Prospective evaluation of the time to peak effect of propofol to target the effect site in children. Acta Anaesthesiol Scand 2009 Aug;53(7):883-90.

RESULTS

After IRB approval and informed consent/assent if indicated, 36 patients (3 groups; n=12 each) have been recruited thus far. Table 1 shows the demographics, Table 2 sedation dosing and Table 3 the procedural times. For Group-MID-G1 the average time to peak effect was 95s (Figure 1a) and the average peak effect BIS was 70.9 (Table 4). For Group-MID-G2 the average time to peak effect was 100s (Figure 1b) and the average peak effect BIS was 76.7 (Table 4). For Group-FENT-G2 there was no significant drop in the BIS (Figure 1c) and the BIS only fell in 17% of the patients in Group-FENT-G2. In all 3 groups, the average BIS at baseline bolus dose was similar (Table 5). The initial clinical effect BIS ranged from 71 to 77 for MID. A 3 compartmental model pharmacokinetic plot from a G2 Midazolam patient is shown in Figure 2. The peak onset time is shown by the dotted line, indicating the plasma/tissue level at the effect site at the time of midazolam peak clinical effect. Of note, after correcting the onset times due to BIS delay processing, the onset time for MID-G1 was 120 seconds and MID-G2 was 125 seconds

CONCLUSION

From the data collected thus far the time for peak effect MID ranged between 120 to 125 seconds depending on the age. Using a correction factor due to analysis delay in the BIS monitor, which we have previously calculated to be ~ 25s for our model). The peak BIS effect ranged between 70 to 77 which is consistent with moderate sedation. The data collected from the FENT-G2 suggested that Fentanyl has a minimal effect on the BIS, only in a few patients did the BIS actually fall after the Fentanyl bolus. When the additional sedation was given as per the sedation dosing regimen (all cases had overall very similar dosing for the three sedative agents) then the BIS values between the groups were all very similar. Knowing the peak onset time for sedation agents will allow for improved pharmacokinetic modeling especially in children where this data is presently sparse, allowing for safer and/or more effective dosing intervals. Study recruitment in the future will also include Propofol and a Midazolam/Fentanyl combination.

Figure 1a. M G1: ONSET BIS

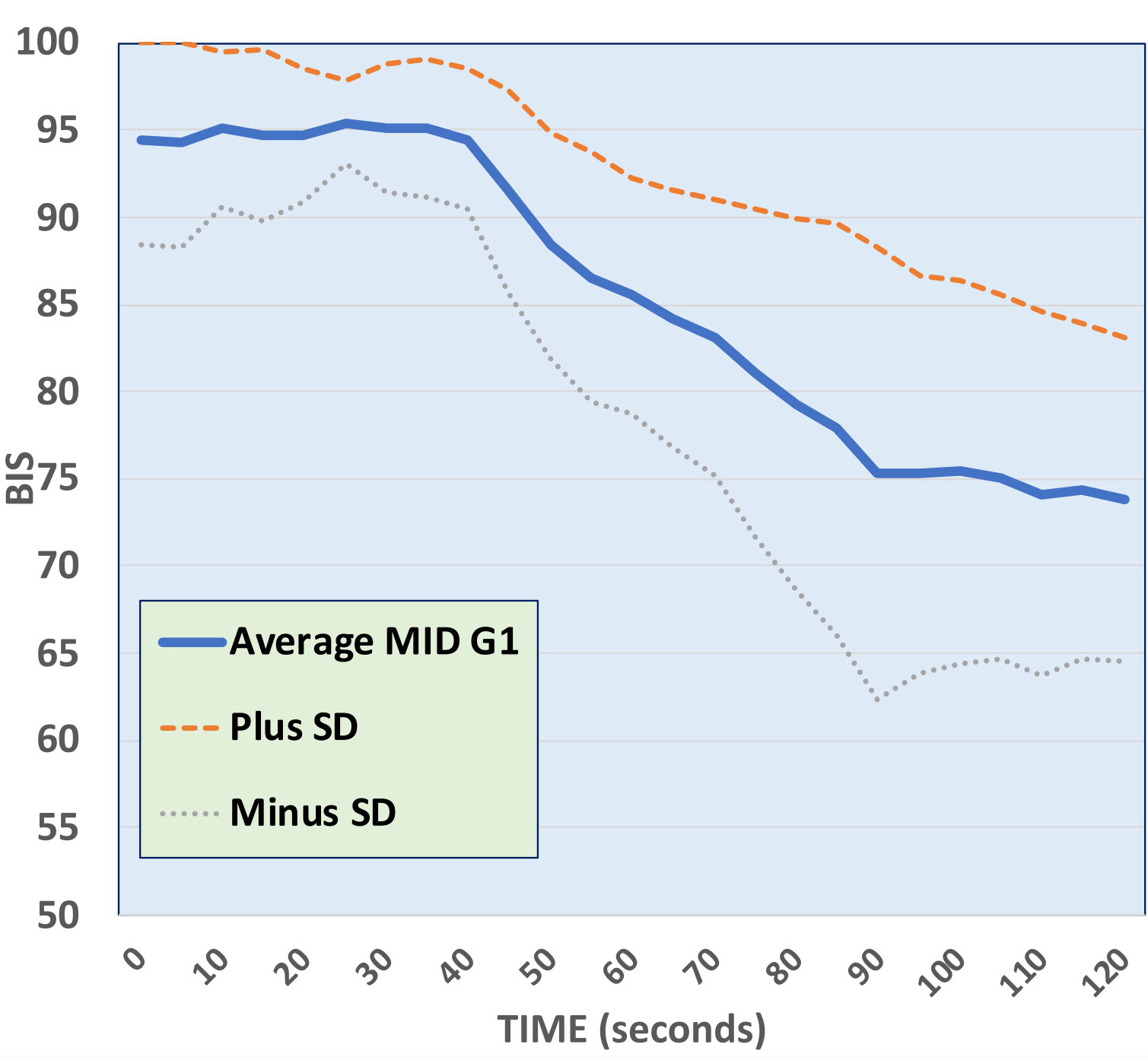


Figure 1b. M G2: ONSET BIS

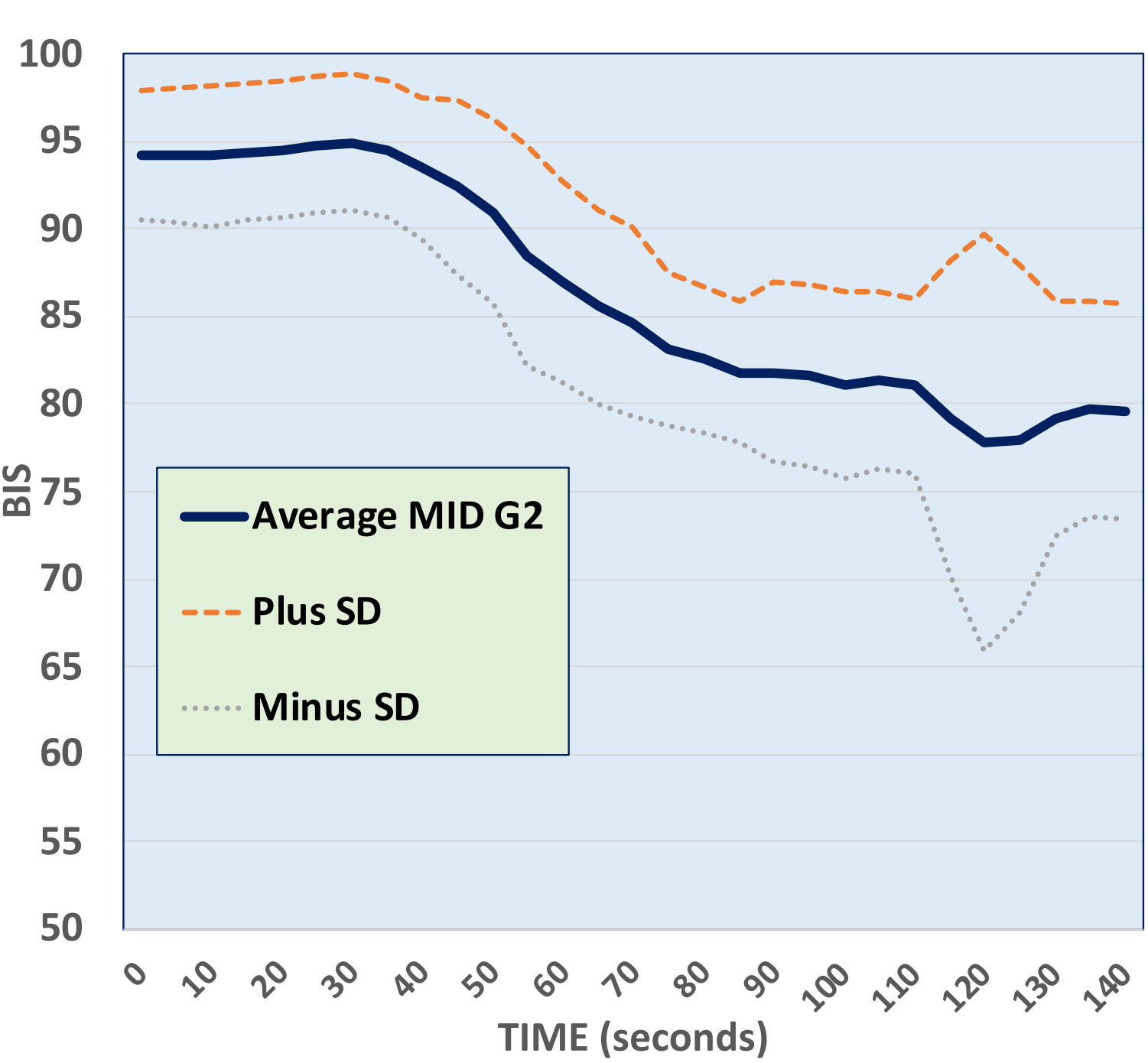


Figure 1c. F G2: ONSET BIS

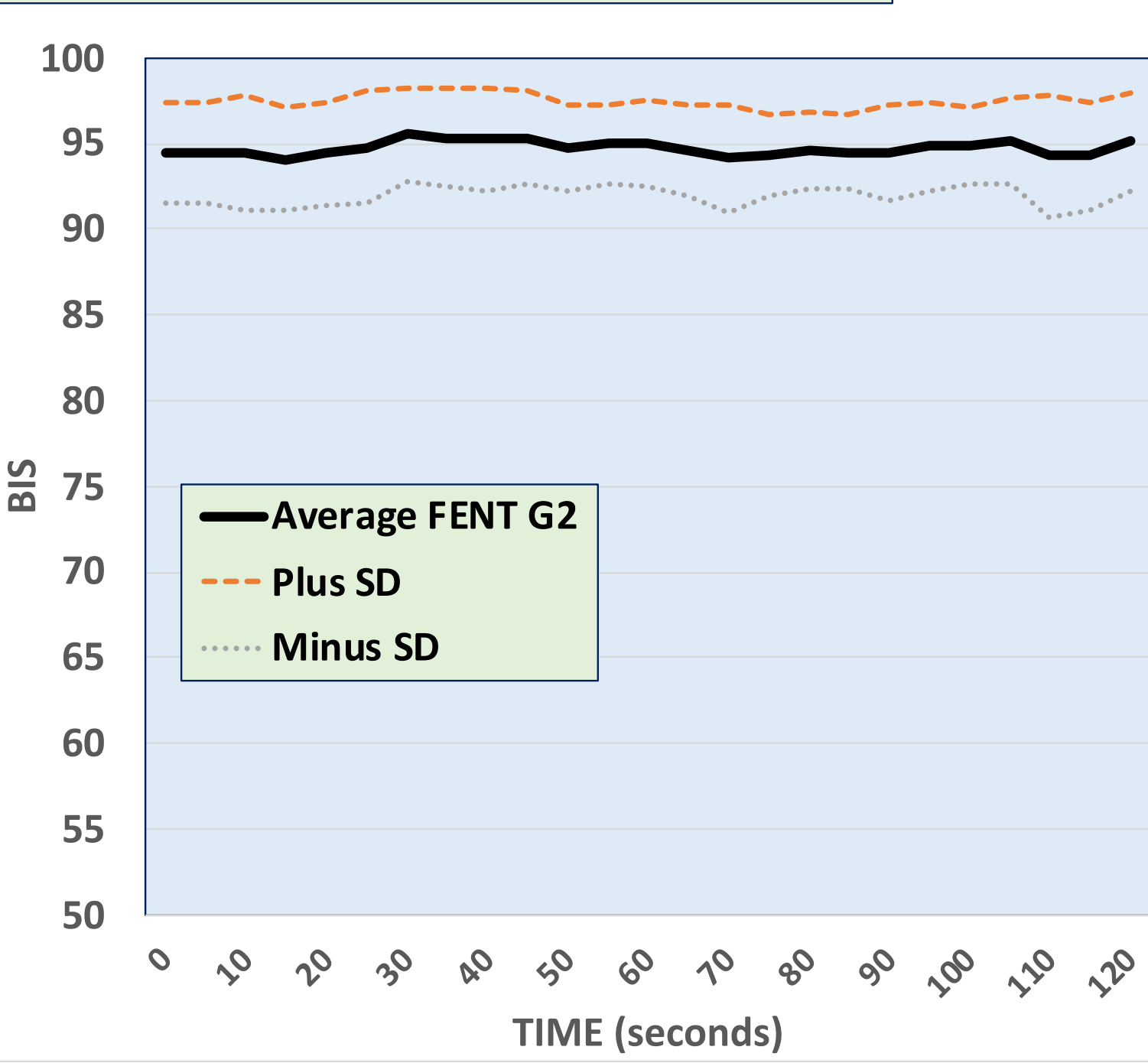


Figure 2. M G2, Case 3

