United States Food and Drug Administration Study, Falck Medical, Inc FMAT1 Compared to Calibrated Weight Indentation Tonography. Copyright 2012

Introduction:

The Falck Medical, Inc. FMAT1 device measures intraocular pressure (IOP), ocular pulsatile amplitude (OPA), the force required for pulsation of the central retinal artery (ophthalmodynamometry-OPH) and aqueous outflow (tonography - TON). The primary cause of glaucoma is impaired outflow of aqueous humor. All current standard of care pharmacological and surgical treatments of glaucoma are designed to increase aqueous humor outflow. Thus, it is important to be able to measure outflow facility to determine therapeutic efficacy. Measuring IOP is not an accurate assessment of therapeutic response. Aqueous humor production and IOP vary diurnally. In glaucomatous and normal eyes there is no scientific evidence that aqueous humor outflow (Tonography) varies diurnally. (Becker – Shaffer's Diagnosis and Therapy of the Glaucomas. 1989. Sixth Edition, Chandler and Grant's Glaucoma. 1997. Fourth Edition.)

The FMAT1 device uses the method of tonography to measure conventional outflow facility. During tonography, the force applied, corneal indentation and applanation area are monitored and recorded by the microprocessor and the optical system. Actively recording and monitoring force application, corneal indentation and applanation area is a significant improvement over existing indentation tonographers. The FMAT1 device also monitors central corneal contact. The only skill required by the technician or doctor is to initially place the prism in central contact with the cornea. The measurement process is initiated with central cornea contact. The measurement is automated and independent of the user.

Three individual IOP measurements consisting of multiple samples obtained every 7 milliseconds are used to calculate an average IOP measurement. For example, an individual average IOP reading of 16 mmHg consists of approximately 60 samples. Within each individual IOP measurement, the samples are analyzed for

repeatability and accuracy (Step 1 analysis). If acceptable, an average IOP is calculated. In Step 2 analysis each individual average IOP measurement is analyzed for repeatability and accuracy. The maximum allowable variation for Step 1 and 2 analyses is 10%. Step 1 and Step 2 analysis criteria must be met, otherwise the FMAT1 device will prompt for a repeat measurement. The same process is used to evaluate applanation area, force application and corneal indentation. Acceptable measurements are displayed on the CDU with percent variation. Using this process, the measurement is user independent.

The FMAT1 device employs a fixed use disposable prism that is an absolute barrier to the transmission of infectious disease.

Methods:

The FDA FMAT1 Tonography clinical study was a single site, single investigator, blinded prospective Institutional Review Board approved study. Study oversight and monitoring was provided by an external Contract Review Organization (CRO) and the staff of the Ophthalmic Division of the US Food and Drug Administration (FDA). Study data analysis was done by the FDA and the independent CRO. Ninety-one subjects and ninety-one eyes were enrolled into the study. The ninety-one subjects (eyes) were coded by a numeric ID and entered into a secure electronic data base. All measurement output went into this secure electronic database. All measurements were performed by two trained ophthalmic technicians. Two different FMAT1 (FMAT1A, FMAT1B) devices were used in the study for comparison to the Model 30 Tonographer. Before each measurement the FMAT1 device performs a calibration routine. All FMAT1 devices calibrate to the same internal standards. The Model 30 Tonographer was calibrated before each use according to the user instruction manual. None of the devices used in the study failed calibration at any time.

Two groups of eyes were enrolled for the study. In Group A, sixty-one eyes with a diagnosis of glaucoma (open angle or closed angle) or ocular hypertension were enrolled. The criteria for the diagnosis of glaucoma was glaucomatous nerve fiber

layer defects documented by computerized tomography (Heidelberg Retinal Tomograph, HRT2), glaucomatous visual field defects documented by computerized visual field testing (Zeiss Humphrey 30-2 Program) and a history of elevated IOP (>24 mmHg). Additionally, for the diagnosis of closed angle glaucoma, on direct gonioscopy the drainage angle was closed. For the diagnosis of ocular hypertension, the eye enrolled had an IOP greater than 24 mmHg without any glaucomatous findings. Thirty eyes had open angle glaucoma, eight eyes had angle closure glaucoma and twenty-three eyes had ocular hypertension.

The average age of Group A subjects was 65.7 +/- 13.0 years and the average age of Group B subjects was 64.3 +/- 8.7 years which was not statistically significantly different, $p = 0.60$. In Group A there were 38 females and 23 males. In Group B there were 24 females and 6 males.

The measurement sequence FMAT1 versus Model 30 changed every five eyes. Intra-visit FMAT1 variability, inter-visit FMAT1 variability and FMAT1A and FMAT1B intra-visit variability analysis was performed. Operator effect was also analyzed. External independent statistical analysis was provided by Synectechs, Inc., who was blinded as to which was the normal group and which was the glaucoma group. All eyes were used in the analysis. There were no screen failures, no loss to follow-up and no adverse events.

The clinical study was conducted in accordance with the abbreviated rules for investigational device exemptions within the meaning of 21 CFR Part 812.2(b), with the rights and protections of investigational subjects in accordance with 21 CFR Part 50-Informed Consent and 21 CFR Part 56-Instituitional Review Board Regulations. Institutional Review Board approval was granted on February 16th, 2010. For further protocol details see Section 14.4.

Results:

In Group A, on computerized visual field testing the average pattern standard

deviation defect was 3.67 +/- 4.1 db, range 1.1 to 20 db and the average mean defect was – 3.0 +/- 3.6 db, range –15.4 to 1.2 db. The average IOP (Po) was 20.02 +/- 5.5 mmHg with a range of 12.9 to 42 mmHg. The average outflow facility (C) was 0.09 +/- 0.05 ul/minute with a range of 0.01 to 0.22 ul/minute.

In Group B the documented IOP was consistently less than or equal to 24 mmHg and none of the thirty eyes enrolled had no examination findings consistent with the diagnosis of glaucoma. Additionally, none of the subjects had any known glaucoma risk factors. Thirty eyes were enrolled in Group B. The average IOP (Po) was 18.7 +/- 2.4 mmHg with a range of 14.6 to 24 mmHg. The average outflow facility (C) was 0.31 +/- 0.12 ul/minute with a range of 0.16 to 0.6 ul/minute. Two repeat measurements on each of the ninety-one subject eyes were taken with the FMAT1 device for a total of 182 outflow facility measurements. Sixty measurements were in the low outflow range of 0.01 to 0.095, sixty-one in the middle range of 0.10 to 0.17 and sixty-one in the high range of 0.18 to 0.6 ul/minute.

The difference in IOP and outflow facility between Group A and Group B was statistically significant, 20.02 +/- 5.5 vs. 18.7 +/- 2.4 mmHg, p=0.0221 and 0.09 +/ - 0.05 vs. 0.31 +/- 0.12 ul/minute, $p < 0.0001$.

Intra-visit Variability Analysis:

Two separate repeat IOP (Po) and outflow facility (C) measurements were obtained with the FMAT1 device during the same visit. There was no statistically significant difference between the first measurement versus the second measurement for IOP and outflow facility, 18.65 +/- 2.46 vs. 18.62 +/- 2.40 mmHg, p = 0.95; 0.31 +/- 0.12 vs. 0.31 +/- 0.12 ul/minute, p=0.99, n=60.

Inter-visit Variability Analysis:

At the initial visit and at the follow-up visit within six weeks, the IOP (Po) and outflow facility (C) was measured with the FMAT1 device. The operator was

blinded to the first visit results. There was no statistically significant difference between the first visit measurement versus the second visit measurement of IOP and outflow facility, 18.66 +/- 2.40 vs. 18.60 +/- 2.46 mmHg, p=0.90;0.31 +/- 0.12 vs. 0.30 +/- 0.12 ul/min, p=0.64, n=60.

Testing Sequence Analysis, FAT1 and Model 30:

The testing sequence, FMAT1 versus the Model 30 changed every five eyes. Distribution and randomness testing of the IOP (Po) and outflow facility(C) measurement difference between the FMAT1 and the Model 30 and the testing sequence was carried out using the Wilcoxon test. The mean difference between the FMAT1 and the Model 30 and the testing sequence for IOP was 0.0009 mm Hg and for outflow facility was 0.0007 ul/min-mmHg. The difference between the IOP and outflow facility measurement obtained with the FMAT1 device versus the Model 30 and the testing sequence was not statistically significantly different, p = 0.61 and 0.86 for the Wilcoxon two-sided test (n=182).

Mean Measurement Difference between the Two Devices:

The mean measurement difference between the Model 30 and the FMAT1 for IOP (Po) was -0.21 mmHg and for outflow facility (C) was -0.006 ul/minute for Group A (n=122), and 0.005 mmHg and -0.001 ul/minute for Group B (n=60).

Ninety-three % and 96% of the Group A paired differences for IOP and outflow facility respectively, are within +/- 1.96 standard deviations of the mean difference. For Group B, 97% and 93% of the paired differences for IOP and outflow facility respectively, are within +/- 1.96 standard deviations of the mean difference. Please see the Bland –Altman data plots (Figures 2a) in Section 14.3.

Mean Measurement Difference between Group A and Group B:

The mean measurement difference for IOP (Po) and outflow facility (C) was compared for Group A versus Group B using the FMAT1 and Model 30. For the

FMAT1 device, the measurement difference for IOP (Po) and outflow facility (C) was statistically significantly different between Group A and Group B. Group A IOP was 20.02 +/- 5.5 mmHg and Group B IOP was 18.6 +/- 2.4 mmHg, p =0.0221 (unequal variance). Group A IOP range was 12.9 to 42 mmHg. Group B IOP range was 14.6 to 24 mmHg. Group A outflow facility was 0.09 +/-0.05 ul/minute and Group B outflow facility was 0.31 +/- 0.12 ul/minute, $p < 0.0001$. Group A outflow facility range was 0.01 to 0.22 ul/minute. Group B outflow facility range was 0.16 to 0.6 ul/minute.

For the Model 30 device, the measurement difference for IOP (Po) and outflow facility (C) was statistically significantly different between Group A and Group B. Group A IOP was 19.8 +/- 5.7 mmHg and Group B IOP was 18.7 +/- 1.9, p = 0.047 (unequal variance). Group A IOP range was 14 to 46 mmHg. Group B IOP range was 15 to 22 mmHg. Group A outflow facility was 0.08 +/- 0.04 ul/minute and Group B outflow facility was 0.31 +/- 0.12 ul/minute, $p < 0.0001$. Group A outflow facility range was 0 to 0.21 ul/minute. Group B outflow facility range was 0.16 to 0.6 ul/minute.

Correlation:

The correlation between IOP (Po) and outflow facility (C) measurements obtained with the FMAT1 versus the Model 30 was studied using linear regression analysis. For Group A the linear correlation coefficient was 0.88 for IOP and 0.77 for outflow facility. The null hypothesis that the slope was zero is rejected, $p < 0.0001$. For Group B the linear correlation coefficient was 0.69 for IOP and 0.97 for outflow facility. The null hypothesis that the slope is zero is rejected, $p< 0.0001$. See Figures 1a in Section 14.3.

Precision Analysis:

1. Operator plus the Device

The effect of different operators (operator 1 vs. 2) with the same FMAT1 device

with the same eye was evaluated for IOP (Po) and outflow facility (C) using ANOVA. No significant operator effect was found for IOP (p= 1.0) or outflow facility (p= 0.99).

2. Same Operator with Different Devices

The effect of different devices, FMAT1A versus FMAT1B, with the same operator and the same eye was examined for the measurement of IOP (Po) and outflow facility (C) using ANOVA. No significant device effect was found for IOP (p=0.96) or outflow facility (p=0.94).

3. Replicate Analysis, Same Operator, Same Device

The repeat measurement difference for IOP (Po) and outflow facility (C) with the same operator, same FMAT1 device and same eye was examined using ANOVA. No significant repeat measurement difference was found for IOP (p=0.95) or outflow facility (p=0.99).

Conclusion:

The clinical study results demonstrate the safety, precision, accuracy and repeatability of the FMAT1 device. The ability of the FMAT1 device to discriminate between glaucomatous and non-glaucomatous eyes is also demonstrated. The clinical study confirms the relationship between the severity of glaucoma and impaired outflow facility. Eyes with advanced glaucoma had Outflow Values of less than 0.09 ul/mmHg and eyes with moderate glaucoma had outflow values of 0.10 to 0.17 ul/mmHg.