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Sensitivity and Specificity of Non-Invasive Blood Glucose Level Measurement Optical Device to Detect Hypoglycaemia

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Summary Hypoglycemia is related to lethargy, psychiatric disorders, and impaired brain metabolism. Hypoglycemia is one of the leading factors of death in blood glucose level (BGL) metabolism disorders. Optical methods have been heavily researched due to its potential to eliminate drawbacks of conventional hypoglycemia detection; however, clinical data are still scarce. This study objective was to measure the sensitivity and specificity of non-invasive BGL Measurement Optical Device (NI-BGL-MOD) to detect hypoglycemia. The reference standard is venipuncture spectrophotometry. Researcher has developed NI-BGL-MOD, which we have used in a clinical trial in December 2015. The researchers have used spectral data collected from the device to measure the BGL of randomly selected 110 participants who were older than 17 y old. Each participant was measured five times. There are a total of 550 data sets that were then compared to BGL measurement using the reference standard. The spectral data were optimized using Discrete Fourier Transform and inferred to BGL prediction using the Fast Artificial Neural Network. Researchers have defined hypoglycemia case with BGL level at 75 mg/dL or lower. The researchers have calculated sensitivity and specificity using epiR in Rstudio. Respondents' BGL values were between 67 to 96 mg/dL. Researchers have classified eighty-nine cases as hypoglycemia. There are 461 cases classified as not hypoglycemia. The sensitivity was 54%, and the specificity was 97%. Diagnostic accuracy was 86%, and the number to diagnose was 1.96. The newly developed method NI-BGL-MOD could be used to detect hypoglycemia.

Key Words non-invasive, blood glucose level, measurement, optical device, hypoglycemia

Hypoglycaemia is a state of decreased blood glucose level (BGL) or concentration in human blood (*1*). Hypoglycaemia is related to lethargy (*2*), psychiatric disorders (*3*), and impaired brain metabolism (*4*).

Hypoglycemia is one of the leading factors of death in BGL metabolism disorders. Patients experiencing severe hypoglycemia were at higher risk of CV events and death. The risk particularly high shortly after the hypoglycemic episode (*5*). Recurrent induced hypoglycaemia may cause severe hypoglycaemia. Other related risks include hypoglycemic arrhythmic death and vascular diseases (*6*). Hypoglycemia mediated effects may contribute to cardiovascular dysfunction. Hypoglycaemia could cause Qt interval prolongation. Hypoglycaemia related to increased plasma epinephrine and norepinephrine concentrations. Hypoglycaemia related to hypokalemia. Hypoglycaemia related to changes to cardiac workload and heart rate. Hypoglycaemia may cause a fall in central arterial pressure and large vessel elasticity. Hypoglycaemia related to an increase in endothelial dysfunction and inflammation. Hypoglycaemia related to platelet aggregation and increased blood coagulation (*7*).

BGL measurement is an integral part of nutritional management. Currently, there are no known dependable methods to detect hypoglycaemia and giving a warning system to the patient. Hypoglycaemia can only predict from its a symptom, or measured using conventional blood glucose level measurement. The methods itself based on phlebotomy or blood extraction procedure, which is hurting, risk of disease spread, need skilled person, and relatively costly (*8*). The only currently plausible methods to detect hypoglycaemia is using the Continuous Glucose Monitoring System, which is not portable and costly (*9, 10*).

Optical methods have been heavily researched due to its potential to eliminate drawbacks of conventional hypoglycemia detection; however, clinical data are still scarce (*11, 12*). The researcher has done a clinical trial of non-invasive methods to non-invasively measure the blood glucose level in 2016 (*13, 14*). Then the

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Researcher realises the possibility of using the same methods to detect the hypoglycaemia.

This study objective was to measure the sensitivity and specificity of non-invasive BGL Measurement Optical Device (NI-BGL-MOD) to detect hypoglycemia. The researchers have used venipuncture spectrophotometry as a reference standard.

MATERIALS AND METHODS

This research is an experimental research using secondary data taken from a previous clinical trial of NI-BGL-MOD (*15, 16*). Researcher team have designed the NI-BGL-MOD in 2015 (*13, 14*). The Clinical team did the clinical trial in December 2015, and the team has done the data analysis in 2018. The research team has registered the clinical trial to Health Research Ethical Committee, National Institute of Health Research and Development, Indonesian Ministry of Health; no LB.02.01/5.2/KE.493/2016).

The researchers have used spectral data collected from the device to measure the BGL of 110 participants. Participants were older than 17 y old, did not tired, having alcoholic drinks, smoking, nor pregnant. Each participant was measured five times. Five hundred fifty data sets compared to BGL measurement using reference standard.

The spectral data were optimized using Discrete Fourier Transform (*17*) and inferred to blood glucose level prediction using Fast Artificial Neural Network (*18*). The researcher has defined hypoglycemia case with BGL level at 75 mg/dL or lower (*1*). The researchers have calculated sensitivity and Specificity (*19*) using epiR (*20*) in Rstudio (*21*).

RESULTS

Respondents' BGL values were between 67 to 96 mg/dL. The researchers have classified Eighty-nine cases as hypoglycemia. Four hundred sixty-one cases have classified as not hypoglycemia (Table 1).

The sensitivity was 54%, and the specificity was 97%. Diagnostic accuracy was 86%, and the number to diagnose was 1.96 (Table 2).

DISCUSSION

NI-BGL-MOD Specificity at 97% shows that practitioner may use NI-BGL-MOD method for detecting hypoglycaemia. However, sensitivity at 54% leaves room for further improvement.

Current methods for detecting hypoglycaemia using apparent clinical symptom observation, like using dogs (*22*), still outdone NI-BGL-MOD methods in the substantial margin at the specificity of 97.9%. Measure insulin concentration remain the best choice for detecting hypoglycaemia at a sensitivity of 97.5% and specificity of 100% (*23, 24*). Periodical data observation dependent methods such as statistical methods (*25, 26*) and machine learning-based methods (*27, 28*) gave a comparable performance to our methods (Table 3).

The number needed to diagnose at 1.96 means at a minimum, only two repeated measurements needed

Table 1. Base prevalence of hypoglycaemia. Hypoglycaemia detected using NI-BGL-MOD. The value then compared to venipuncture measurement.

| NI BGL MOD | Veni Puncture | | Total |
	Positive Hypoglycaemia	Negative Hypoglycaemia	
Positive Hypoglycaemia	78	11	89
Negative Hypoglycaemia	67	394	461
Total	145	405	550

Table 2. Sensitivity and specificity of NI-BGL-MOD for hypoglycaemia detection.

| Parameters | 95% Confidence Interval | | |
	Estimation	Lower	Upper
Apparent Prevalence	0.162	0.132	0.195
True Prevalence	0.264	0.227	0.303
Sensitivity	0.538	0.453	0.621
Specificity	0.973	0.952	0.986
Diagnostic Accuracy	0.858	0.826	0.886
Diagnostic Odd Ratio	41.7	21.1	82.5
Number Needed to Diagnose	1.958	1.646	2.468
Youden Index	0.511	0.405	0.607
Positive Predictive Value	0.876	0.790	0.937
Negative Predictive Value	0.855	0.819	0.886
Likelihood Ratio of a Positive Test	19.81	10.85	36.16
Likelihood Ratio of a Negative Test	0.475	0.398	0.567

Table 3. Comparison of sensitivity and specificity of methods to detect hypoglycaemia.

| Hypoglycaemic Detection Methods | 95% Confidence Interval | | |
	Sensitivity	Specificity	Reference
NI-BGL MOD	54%	86%	This trial
Measurable Biomarker	89%	100%	(*23*)
	98%	92%	(*24*)
Clinical Symptom Observation		98%	(*22*)
Statistical Data Observation	84%	82%	(*25*)
	89%	86%	(*26*)
Machine Learning Data Observation	78%	60%	(*29*)
	80%	50%	(*30*)
	80%	98%	(*28*)
	69%	97%	(*27*)

to diagnose hypoglycaemia accurately. The current designed NI-BGL-MOD is taking five measurements sequentially and take the average, which is sufficient.

NI-BGL-MOD eliminate the use of phlebotomy to extract human blood from the central vein or peripheral vein in conventional biomarker measurement method. NI-BGL-MOD make use of minimal human auditory capabilities to detect hypoglycaemia, as opposed to clinical symptom observation. NI-BGL-MOD rely on non-invasive measurement rather than observation of data series, as opposed to a statistical or machine-learning data-observation method (29, 30).

The current clinical trial data came from cross-sectional or one-time measurement data, as opposed to array periodical measurement, so. In contrast, the system designed to detect hypoglycaemia, further clinical trial needed to detect the timing for such instance. The current clinical trial data came from cross-sectional or one-time measurement data, as opposed to array periodical measurement, so. In contrast, the system designed to detect hypoglycaemia, further clinical trial needed to detect the timing for such instance.

Therefore, the artificial intelligence or machine learning engine is similar to those used on the periodical data observation method. However, the current system does not yet to have the capabilities to detect when the hypoglycaemic instance shall occur.

Based on the evidence shown from the current study, the researchers concluded that the newly developed method NI-BGL-MOD could be used to detect hypoglycemia.

Researchers are planning to conduct one further clinical trial in 2020. The trial shall use an oral glucose tolerance test setting (31, 32) to further elaborate NI-BGL-MOD methods potential for detecting hypoglycaemic event timing.

Disclosure of state of COI

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