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Development of an Artificial Intelligence Algorithm to Predict Hypotension Risk After Induction in Cesarean Sections With Spinal Anesthesia

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1.Study Type: Non-Interventional Single-Center Prospective Observational Clinical Study

2.Location of the Study:

Evaluation of patients for eligibility for the study, recording of preoperative demographic information and vital signs, collection of blood samples, and administration of spinal anesthesia: Hacettepe University Hospital, Section 81 Delivery Room

Evaluation of blood samples: For all samples except Syndecan-1, Hacettepe University Adult Hospital, Department of Biochemistry Central Laboratory; for Syndecan-1 samples, Hacettepe University Faculty of Medicine, Department of Biochemistry Laboratory will be used.

Recording, defining, and cleaning of data: Hacettepe University Faculty of Medicine, Department of Anesthesiology and Reanimation

3.Timing of the Study:

Ethical approval for the project has been granted by the Hacettepe University Non-Interventional Clinical Research Ethics Committee as of January 25, 2023. The study is planned to be conducted between December 2023 and March 2024.

4.Universe, Sample, and Research Group of the Study:

4.1. Inclusion criteria:

- Being 18 years of age or older
- Having an American Society of Anesthesiologists (ASA) physical status of I, II, or III
- Being at a gestational age of 37 weeks or more
- The patient having received spinal or combined spinal-epidural anesthesia

4.2. Exclusion criteria:

- The patient's refusal to participate in the study
- Multiple pregnancy
- Emergency cesarean
- The patient being preeclamptic

- Preoperative systolic blood pressure equal to or greater than 140mmHg (hypertensive patient)

- Having a contraindication to spinal anesthesia or failure of spinal anesthesia

5. Methods and Data Collection Tools of the Study:

Data from patients meeting the inclusion criteria in Section 81 Operating Room will be obtained from the results of routine tests sent after hospitalization for cesarean section, preoperative nurse observation forms, and records of vital signs monitored by anesthesia during surgery. After the patient is taken to the operating room, the "Data Collection Form" under the title "Appendix-1" will be filled out by the anesthesiologist. The duration of hypotension after spinal anesthesia in pregnant women starts immediately after the anesthesia application and reaches the lowest level within approximately 10-15 minutes. Then, it is known to return to normal within 20-30 minutes. However, the duration of hypotension can vary depending on the gestational week, anesthesia dose, the patient's general health condition, and other factors. Especially in pregnant women with high blood pressure or those who receive high doses of anesthesia, the duration of hypotension can be longer. Therefore, the duration of hypotension should be evaluated separately for each patient. However, for this study, it has been preferred to observe for the first 15 minutes. This choice has been made because the algorithm is intended to predict hypotension induced by spinal anesthesia based on preoperative characteristics. With an extended observation period, it is clear that hemodynamics become a complex situation influenced by multiple independent factors, such as childbirth, increased cardiac output, and the initiation of oxytocin infusion during surgery. The data collection process will end after the first 15 minutes. Hypotension data developing after the 16th minute will not be recorded, and the study-specific observation will be terminated.

6.Data Collection for the Study:

The number of patients needed to develop an artificial intelligence algorithm can vary depending on the characteristics of the data sources used, the complexity of the algorithm, and the projected accuracy level. However, larger and more diverse data sets generally provide more accurate results. Many studies in the literature emphasize the importance of large data sets in the development of artificial intelligence algorithms. For this purpose, the frequency of hypotension after spinal anesthesia in cesarean sections varies in the literature, but it has been observed that the frequency does not exceed 75%. In light of these studies, the sample size of the study has been calculated using power analysis based on the following formula:

$$\frac{Z_{1-\alpha/2}{}^2 \times p \times (1-p)}{d^2}$$

Z: Standard normal deviation. (For a type 1 error of 5% (P<0.05), it is 1.96, and for a type 1 error of 1% (P<0.01), it is 2.58). In this study, it has been determined as (P<0.05).

P: The expected ratio, based on previous studies or pilot studies, has been determined as 75%, as explained in the literature.

d: The absolute error or precision has been determined as 0.05.

Based on this information, the minimum number of patients to be included in the study has been determined to be 280, with a type 1 error rate below 5%, a disease addition rate of 75%, and an absolute error of 0.05.

Before the patients are taken to the operating room, enough blood will be separated from the routine pre-delivery blood samples for the blood parameters listed in the "Data Collection Form" under the title "Appendix-1." Other parameters in the blood parameters besides Syndecan-1 are routinely tested in the biochemistry laboratories of Hacettepe University Hospital.

A commercial kit will be used for the mentioned Syndecan-1 molecule. To detect Syndecan-1 in serum, samples will be taken in yellow-capped, gel tubes and allowed to clot at room temperature for 10-20 minutes. Then, the transport to the Hacettepe University Department of Biochemistry Laboratory will take place, and after centrifugation at 3000 g for 10 minutes, the serum will be separated and aliquoted into eppendorf tubes in appropriate volumes and stored at -80 °C until the day of the ELISA study. Before the ELISA study, the samples will be thawed, and dilution will be done using 0.9% NaCl as deemed appropriate by the kit.

6.1 Routine Obstetric Spinal Anesthesia Practice

No specific intervention will be made regarding the amount of preoperative fluid, but the administered fluid will not be of colloid character (the amount of fluid will be noted). Preoperative fluid loading has been shown to damage the endothelial glycocalyx. Standardized fluid loading has the potential to affect the results of syndecan-1 released into circulation as a result of endothelial glycocalyx damage. The duration of oral fasting is routinely applied worldwide for at least 6-8 hours. This duration will not be specifically standardized, but the 6-8 hour rule will be followed. There will be no intervention in the oxytocin dosage given by the Obstetrics and Gynecology department during the management of the delivery process, and if preoperative oxytocin infusion is given, it will be noted. When the procedure starts, a stopwatch will be started, and the duration of spinal anesthesia will be recorded.

After the patient is taken to the operating room, standard monitoring will be performed with electrocardiogram, non-invasive blood pressure, and pulse oximetry;

the patient's initial pulse, non-invasive blood pressure, saturation values, vertebral column, and abdominal circumference lengths will be recorded. Since patients usually come to surgery with an intravenous line in place, a bolus of 10 ml/kg fluid and maintenance fluids (a total of 1000 ml crystalloid administration) will be given through the existing vascular access. After standard monitoring, the patient will be positioned sitting for marking and anesthesia application. The highest line connecting the right and left iliac crests (Tuffier's line) is determined as the entry site for the L3-L4 interspinous space or L2-L3 space through conventional palpation of anatomical landmarks. In patients with successful spinal entry, spinal anesthesia is achieved with LA doses and types shown in Table 1, appropriate for the patient (intrathecal 10-12 mg bupivacaine and 15-25 mcg fentanyl added). The block level is determined by the ice test/pin prick test 10 minutes after the procedure is completed and the patient is placed in the supine position. Blocks reaching the T4-T6 level are considered successful, and surgery is started.

The type and dose of local anesthetic to be used during spinal anesthesia are shown in Table 1:

Length (cm)	**Bupivacaine 0.5% (Izobaric) (mg)**
150-160	8
160-180	10-12.5
>180	12.5-15

Table 1: Local anesthetics to be used in cesarean delivery performed with subarachnoid block.

At the start of spinal anesthesia, the patient will begin to receive a crystalloid fluid between 1000 ml (co-load) that will end during the operation. Only this fluid will be given during the operation, and in case of hypotension, treatment will be done with ephedrine as a vasopressor. IV boluses of 5-10 mg will be given until hypotension is corrected, and if necessary, hypotension will be intervened with an infusion of 1-5 mg/min[32]. The decision for ephedrine or other treatments will not be influenced by the data collection process. The patient will be observed for 15 minutes from the time of supine placement, and hypotension will be noted when it occurs. The definition of hypotension for this study is made as any of the following conditions:

- Mean arterial pressure dropping below 65mmHg
- Systolic Blood Pressure dropping below 80 mmHg
- Systolic Blood Pressure dropping below 75% of the baseline value

- The emergence of hypotension symptoms such as dizziness, increased salivation, dyspnea, nausea, vomiting.

During the study, there will be no changes in treatment approach based on the data for algorithm development. In the process of developing artificial intelligence, no patient's treatment will be influenced by this process. There will be no changes in anesthesia management with the study. Routine anesthesia management will be performed, and only the results will be observed.

6.2. Analysis of Syndecan-1 in Patient Serums:

Syndecan is a proteoglycan molecule, and its serum levels will be measured using the enzyme-linked immunosorbent assay (ELISA) method with a commercial kit.

In the sandwich ELISA method to be used, there is a two-step binding process. The first is between the primary antibody covalently bound to the solid surface of the measurement plate and the antigen (Syndecan-1). After a washing process to remove unbound molecules, the second stage of binding is completed by adding a secondary antibody solution specific to the primary antibody. This second antibody is conjugated with the horse radish peroxidase enzyme, and quantification is targeted through spectrophotometry by adding 3,3′,5,5′-tetramethylbenzidine as a substrate.

The absorbance reading on the measurement plate will be performed with the SpectraMax-M2 (Molecular Devices, USA) device located in the Department of Medical Biochemistry and then serum Syndecan-1 levels will be calculated using the GraphPad Prism program based on the standard graph.

In a study measuring serum Syndecan-1 levels in a healthy population, the median value was found to be 0.3 ng/mL[34]. Syndecan-1 levels increase during pregnancy, reaching levels of 38 ng/mL in the last period of pregnancy.

The Syndecan-1 ELISA measurement kit to be used in this study will be carefully chosen to be sensitive enough for the study in serum and the coefficient of variation in repeated measurements will be below 10%.

7. Analysis of Data:

The Python Programming Language will be used in all stages of algorithm development. The "Guidelines for Developing and Reporting Machine Learning Predictive Models in Biomedical Research: A Multidisciplinary View." guideline will be followed in the process of developing the artificial intelligence algorithm. The stages are as follows:

7.1. Data Collection: Data will be recorded by filling out the "Data Collection Form."

7.2. Data Processing: After data collection, the data will be processed, randomly divided into training data and internal validation data. The data will be cleaned of artifacts and incorrect readings.

7.3. Labeling (Annotation): Data will be labeled for classification by artificial intelligence, and the definition of hypotension will be made (Annotation). Studies will be conducted to determine the potential of artificial intelligence in detecting hypotension.

7.4. Feature Selection: Features that predict annotated events at the highest rate will be selected. One or more feature selection algorithms will be used for this process, and features will be used based on the success achieved in the models.

7.5. Building the Model: The most related features in the data will be selected, and a model will be developed. After the formation of the data in the study, basic performance rates will be obtained using basic classification algorithms such as K-nearest neighbors, Support Vector Machines (SVM), Decision Trees, Random Forest, which are used for classification processes in the literature. Then, a deep learning method will be developed. The performance difference between the proposed method and the basic methods will be examined.

7.6.Cross-Validation: The performance of the first version of the model will be subjected to cross-validation repeatedly with subsets of data that the model has never seen before. Thus, the performance changes of the proposed method due to data variation will be examined, and the model's success will be determined. Depending on the number of data, either 10-Fold Cross-Validation or 5-Fold Cross-Validation method will be used.

7.7. Test of the Model: The predictive performance of the algorithm trained with training data will be demonstrated with internal validation data that it has never seen before .

In addition to the algorithm development process, if the variables are normally distributed, the analysis of the monitored numerical variables will use "ANOVA", "Student's t-test", and "Mann Whitney U test" depending on the number of groups compared and the analysis of normal distribution of variables. For the relationship between hypotension values and other continuous parameters, "Pearson Correlation Analysis" and "Spearman Correlation Analysis" will be used depending on the analysis of normal distribution of variables. Moreover, the predictability of the system will be tested with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR), risk ratio (RR), area under the receiver operating characteristic curve (AUROC), and Pearson correlation coefficient (r) tests. The level of statistical significance will be accepted as $p<0.05$. For statistical analysis,

Statistical Packages for the Social Sciences v26.0 (SPSS Inc., Chicago, IL) software will be used.

8. Accuracy Metrics

Sensitivity, specificity, and accuracy are commonly used metrics to measure model performance in classification problems in the medical field. These metrics play a significant role in the detection of diseases such as hypotension.

8.1. Sensitivity: Sensitivity is the true positive rate and is the percentage of true positive predictions out of the total positives. It shows how many of those with the disease are correctly identified. Sensitivity is important for minimizing false negative predictions.

8.2. Specificity: Specificity is the true negative rate and is the percentage of true negative predictions out of the total negatives. It shows how many of those without the disease are correctly identified. Specificity is important for minimizing false positive predictions.

8.3. Accuracy: Accuracy is the ratio of correct predictions to the total number of samples and shows how accurately a model makes predictions. It shows how many of those with and without the disease are correctly identified. However, accuracy can be misleading in situations such as imbalanced class distribution.

In the detection of hypotension, sensitivity and specificity metrics are of great importance. Sensitivity ensures the correct identification of patients with hypotension and minimizes false negative predictions. Specificity ensures the correct identification of patients without hypotension and minimizes false positive predictions.

For example, when developing a machine learning model for hypotension detection, evaluating sensitivity and specificity metrics is important. High sensitivity and specificity values indicate a model with better performance in hypotension detection. However, having high values for only one of these metrics can sometimes conflict with each other. Therefore, a balance point must be found, and both metrics should have optimum values.

APPENDIX 1

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Date:
Time:

DATA COLLECTION FORM

1. PREOPERATİF DEĞERLENDİRME

A.DEMOGRAPHIC INFORMATION

Patient's Code:

Age: **Height(cm):** **Weight(kg):**

Comorbidities:

COPD:	**YES**	**NO**

Gravidity: **Paridity:** **Gestational Age(weeks) :**

Did hypotension develop in the previous cesarean section?	**Yes**	**No**	**Unknown**

AREA	**LENGHT(cm)**
Columna Vertebralis	
Abdominal Circumference	

Medications:

B. VITAL SIGNS

HR(pulse/min)	**Blood Pressure(mmHg)**	**Temperature(^{0}C)**	**$Sp0_2$(%)**

C.VOLUMe INFORMATION

Fasting Duration (hours)	
Fluid Intake in the Last 8 Hours Preop (ml)	
Fluid Bolus preoperatively(ml)	
Oxytocin Dose Administered in the Last 8 Hours (IU)	

Urine output just before the surgery (ml)	

D. BLOOD PANEL

Hb (g/dL)	
Hct (g/dL)	
Eritrosit (x10^6/ /µL	
MCV (fL)	
ESR (mm/sa)	
RDW (%)	
WBC (x10^3/µL)	
Plt (x10^3/µL)	
Ferritin (ng/mL)	
Transferrin Saturation(%)	
Total Iron Binding Capacity (µg/dL)	
Iron (µg/dL)	

ALT (U/L)	
AST (U/L)	
ALP (U/L)	
GGT (U/L)	
Bilirubin, direkt (mg/dL)	
Bilirubin, total (mg/dL)	
Albumin (g/dL)	
Protein (g/dL)	
Creatinine(mg/dL)	
Uric Acid (mg/dL)	
K+ (mEq/L)	
Na+ (mEq/L)	
Mg++ (mEq/L)	
Cl- (mEq/L)	
Glucose (mg/dL)	

aPTT (sn)	
INR	
D-dimer (ng/mL)	
Fibrinogen(mg/dL)	

Syndecan-1(SDC-1) (ng/mL)	

pH	
Pv02(mmHg)	
PvC02(mmHg)	
BE	
Ca++ (mmol/L)	
Laktat (mmol/L)	

CRP (mg/dL)	
Procalcitonin (ng/mL)	
Transferrin(mg/dL)	

2.SPINAL ANESTHESIA CHARACTERISTICS

Observation period is the first 15 minutes after induction. Terminate data collection after the 16th minute.

DRUG	VOLUME	DOSE
Bupivakain heavy		
Fentanil		
Other		

Duration of Spinal Anesthesia Application (seconds):

Puncture Site: **Number of Punctures :**

Block Level:

Type and Gauge of Needle:

Experience of the Practitioner (Junior Resident/Senior Resident/Attending):

Received Sedation:

Type and Dose of Sedation Medication:

3.POST-INDUCTION CHARACTERISTICS

The Lowest Systolic Blood Pressure		
The Lowest Diastolic Blood Pressure		
MAP(Mean Arterial Pressure)		
Symptome		
At which Minute?		
When did the skin incision occur after induction?		
When was the baby delivered after induction?		
Hypotension Decision	**Yes**	**No**
Hypotension Treatment: Ephedrine / Other /Dose		