PROTHROMBIN TIME & INTERNATIONAL NORMALIZED RATIO IN PEDIATRIC LIVER DISEASE

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Abstract

As we all know that Prothrombin Time (PT) / International Normalized Ratio(INR) is used to assess the extrinsic and common pathway of blood coagulation particularly Factor VII estimation. In the present scenario all the laboratories are doing PT /INR estimation & we all are interpreting the value in the management of patients irrespective of the nature of liver disease. The laboratories doing PT /INR estimation is for monitoring oral anticoagulant (Warfarin) therapy not for liver disease per se . We serially observed the 20 liver disease patients for last six months. Some of them (12) having PT/INR value within normal range & some of them (8) having very high value of PT/INR . These 8 patients having very high PT/INR value improves without any interventions showing the falsely high value of PT/INR . We just want to reflect that PT/INR estimation for liver disease per se & for oral anticoagulation therapy monitoring are two different thing and don’t be panic at first viewing of such very high PT/INR value in liver disease patients.

Key words: Prothrombin Time(PT), International Normalized Ratio(INR), International Sensitivity Index(ISI), International Sensitivity Index Liver Disease (ISI LD), Warfarin, LFT(Liver Function Test).

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INTRODUCTION

Before explaining the theme we just refreshing the steps of hemostasis. There are three phases of hemostasis. 1. Vascular spasm or vasoconstriction (smooth muscle of tunica media contract)

1. The role of vasoconstriction is to reduce blood loss & the injured endothelia get sticky, contact each other from opposing ends and seal off the blood vessel form both ends.

2. Platelet plug formation or platelet aggregation (Positive feed-back loop)

The role of the platelet aggregation or plug is to physically seals the broken blood vessel, actin-myosin complex in the aggregated platelets contract to compact the plug, vasoconstrictors are released from plug: serotonin, epinephrine, thromboxane A2, chemicals are released from plug to stimulate coagulation.

3. Blood coagulation/clotting (Fig-2 describes the steps of blood coagulation)

The transformation of blood from a liquid into a solid gel, formed on the top of the platelet plug, strengthens the platelet plug. Fig-3/4 describes it elaborately.

Events after blood clotting

1. Clot retraction: Platelets contract, squeezing serum from the clot. Serum:plasma without clotting proteins

2. Blood vessel repair: Platelet-derived growth factor stimulates rebuilding the wall of the blood vessel.

3. Fibrinolysis After repair the blood clot is removed. Done by the fibrin digesting enzyme: plasmin. Plasminogen (inactive) → → plasmin (active).

The prothrombin time was discovered by Dr Armand Quick and colleagues in 1935, and a second method was published by Dr Paul Owren, also called the "p and p" or "prothrombin and proconvertin" method. The INR (also known as standardised prothrombin time) was introduced in the early 1960s, by Dr. Jack Hirsh and colleagues at McMaster University School of Medicine, when it turned out that
The blood cells are separated from the liquid part of blood (plasma) by centrifugation. The PT test is performed by adding the patient’s plasma to some source of Tissue Factor or factor III (e.g., a protein, thromboplastin, from homogenized brain tissue) to a test reagent and instrument. It is the relative sensitivity of PT (determined from a given batch/pool of Pt. in laboratories) of thromboplastin to decreases in the Vit. K dependent coagulation factors in comparison with a WHO human thromboplastin standard. The ISI is a numerical value that reflects mechanisms of PT prolongation in liver diseases (DECREASE SYNTHESIS OF FACTORII/VII/IX/X) that differ from those involved in oral anticoagulation (INHIBITION OF VIT-K REDUCTION), and the thromboplastin reagents differ in their sensitivities to these 2 mechanisms. Some laboratories hypothesized that the use of plasmas of patients with liver disease instead of plasmas from patients on oral anticoagulation in the calibration model for thromboplastins.

Calibration Procedure of Thromboplastins for the Definition of the Parameter ISI “LD”. Calibration was performed according to the WHO guidelines for thromboplastins and plasma used to control oral anticoagulant therapy, with the following differences: the use of frozen instead of fresh plasmas and the use of plasmas from patients with liver disease instead of plasmas from patients on stable oral anticoagulation but till now no definitive ISI value for liver disease is available. Characteristics of different Thromboplastin Reagents are given in Table-1.

Time required for clotting of plasma after adding thromboplastin is called PT (N = 12-13 sec, > 16 sec = abnormal, ≥ 20 sec = definite abnormality). Blood collected must be used with in 2 hr if at room temp or with in 4 hr if cold & should be frozen if not used with in this period. Frozen sample should be thawed at 37°C before use. PT measures the activity of factor I, II, V, VII, X. PT dose not prolong until the conc. of these factor is <30% or until fibrinogen <100mg/dl. Isolated PT prolongation indicates factor VII deficiency. Normal value of ISI is 1 to 1.2.
without anticoagulation, 2 to 3 with anticoagulation, 2.5 to 3.5 with intense anticoagulation\textsuperscript{18}. Table-2 demonstrates the PT values in various age groups\textsuperscript{19}.

**PATIENTS AND METHOD:**
Twenty (20) cases were included in this study review in last six months. Inclusion criteria being children admitted to our hospital for liver diseases not taking any anticoagulation. Detailed clinical, hematological & LFT evaluation was done for every patients. Out of 20, 12 patients found to have normal PT / INR (mean=12.37±0.88sec) values and 8 patients were having PT / INR values very high(mean=20.13 ±1.78 sec) reflecting very severe liver failure. But these 8 patients though having high PT / INR, surprisingly improves without any active interventions as the parents were extremely poor. Thanks to the God for their survival, but the thing is to think that was their PT / INR reports were correct, if yes then how they survived & if no then what is the fact. Calculation of mean PT / INR was done by SPSS v 16 software.

**DISCUSSION:**
Out of 20 liver disease patients, 12 having PT / INR values normal & 8 patients showed high PT / INR values. This differences most probably due to ISI values\textsuperscript{20} used by the laboratories or lessly due to false positive\textsuperscript{21} / false negative\textsuperscript{22} results. Table-3 shows how PT / INR values differ according to various ISI values. This table demonstrate at a constant INR value PT value decreases as ISI values increases. Fig-6 demonstrate how different thromboplastins influence the PT ratio and INR. Table-4/5 shows various causes of false positive or negative PT / INR. As the thromboplastins are supplied by different laboratories, the ISI values will be different but unfortunately the ISI values used by different laboratories is for monitoring oral anticoagulant therapy & till date ISI for liver disease(ISI LD) is not available, the PT / INR estimation we are sending is not the ideal one.

**CONCLUSION:**
\begin{itemize}
  \item PT ESTIMATION WITHOUT INR IS MEANINGLESS
  \item INR FOR LIVER DISEASE IS DIFFERENT FROM THAT OF INR FOR ANTICOAGULATION THERAPY
  \item TILL DATE INR FOR LIVER DISEASES NOT AVAILABLE(UNDER RESEARCH)
  \item INR CAN BE USED FOR APTT ESTIMATION , BUT INR MEANS PT ESTIMATION
  \item ISI IS VERY IMPORTANT IN CALCULATION OF INR
  \item ISI IS DIFFERENT FOR LIVER DISEASE & ANTICOAGULATION THERAPY
  \item WE MUST CHECK THE ISI VALUE BEFORE INR ESTIMATION
\end{itemize}

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