Gelatin 4% versus Hydroxyethyl starch (130/0.4): Effect on blood coagulation, Hemostasis , Renal function and platelet aggregation in patients undergoing Major Abdominal Surgery

Thesis

Submitted for fulfilment of the degree of MD in Anesthesiology

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بسم الله الرحمن الرحيم

(وَتِلْكَ الْأَمْثَالُ نَضْرِبُهَا لِلنَّاسِ وَمَا يَعْقِلُهَا إِلَّا الْعَالِمُونَ * خَلَقَ اللَّهُ السَّمَاوَاتِ وَالْأَرْضَ بِالْحَقِّ إِنَّ فِي ذَلِكَ لَآيَةً لِّلْمُؤْمِنِينَ *)

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Dedication

To my father and my lovely family

ABSTRACT

The general purpose of the present study was to compare the efficacy and safety of HES (130/0.4) with that of 4% gelatine when these solutions were used in large doses >20 ml/Kg/day. According to a prospective, random sequence, 40 patients undergoing major abdominal surgery received either HES 130/0.4 (n 20) or gelatin (n 20) until the first postoperative day (POD) to keep central venous pressure between 8-12cm H2o and, standard coagulation variables were measured, Platelet aggregation was induced by adenosine diphosphate and renal function were also measured. The study conclude that administration of a new HES 130/0.4 preparation in patients undergoing major abdominal surgery was not associated with negative effects on haemostasis when compared to patients received gelatin. And there was no difference between the two colloid solutions as regarding renal functions. Thus, this HES solution appears to be a safe alternative plasma substitute for intravascular volume replacement in the abdominal surgical patient.

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Key words: Platelet aggregation - Colloids - Gelatin - Hydroxyethyl starsh

LIST OF CONTENTS

List of Tables

List of figures

List of abbreviations

ADP	Adenosine diphosphate
APP	Amyloid precursor proteins
ARF	Acute renal failure
ATPase	Adenosine triphosphatase
BUN	Blood urea nitrogen
Cl	Chloride
CVE	Compensatory intravascular volume expansion
Da	Dalton
DIC	Disseminated intravascular coagulopathy
DS	Degree of substitution
ECV	Extra cellular volume
FDA	Food and Drug Administration
HES	Hydroxyethyl starches
ICV	Intracellular volume
IFV	Intracellular fluid volume
K	Potassium
KD	Kilo Dalton
Kg	Kilogram
Mg	Milligram
mOsm	mili-osmole
Mw	Molecular weight
Na	Sodium
NADH	Nicotinamide adenine dinucleotide reduced form

PAF	Patelet activating factor
PAIs	Plasminogen Activator Inhibitors
PAIs	Plasminogen Activator Inhibitors
Pas	Plasminogen Activators
PDGF	Platelet-derived growth factor
PFA-100	Platelet function analyzer-100
PF4	Platelet factor 4
PKC	Protein kinase c
PPP	Platelet-poor plasma
PRP	Platelet-rich plasma
PV	Plasma volume
PVE	Plasma volume expansion
RBCV	Red blood cell volume
ROTEG®	Rotational Thromboelastograph
t-PA	Tissue-type Plasminogen Activators
TEG	Thromboelastogram
TFPI	Tissue Factor Pathway Inhibitor
TGF-B_1	Transforming growth factor B_1
U-PA	Urokinase-like Plasminogen Activators
VEGF	Vascular endothelial growth factor
vWF	Von Willebrand factor

Introduction

Synthetic colloids are increasingly used as plasma substitutes in hypovolemic patients because they are readily available, carry no risk of transmitting viral or other plasma transfusion-related disease, and are relatively inexpensive .[(1)]

Controversy exists over whether colloids or crystalloid solutions should be used as plasma expander .Advocates of colloids argue that hypo-oncotic crystalloids leak from the plasma to excessively expand the interstitial fluid volume, whereas crystalloid supporters argue that leakage of colloid into the interstitial space contributes to edema formation .[(2)]

Colloid solutions used in clinical practice for fluid therapy are divided into the semisynthetic colloids [gelatins, dextrans, and hydroxyethyl starches (HES)] and the naturally occurring human plasma derivatives (human albumin solutions, plasma protein fraction, fresh frozen plasma, and immunoglobulin solution).[(3)]

Gelatin appear to be without adverse effects on kidney function, however, HES may cause kidney dysfunction. Acute renal failure was reported when patients with impaired renal function received very high molecular weight (Mw) HES (Mw 450,000 D, DS 0.7) and in case of pre-existing alternations of renal function, the use of low-molecular-weight and low substitution-ratio HES is not associated with a decline in renal function.[(4)]

All commercially available synthetic colloids interfere with normal haemostasis by a non-specific effect (hemodilution), and specific effect depending on the type of compound. Several recent *in vitro* and *ex vivo* studies have questioned the generally accepted belief that gelatins have no specific effects on hemostasis. Indeed, both modified fluid gelatin and urea-linked gelatin have been shown to significantly impair ADP-induced platelet aggregation, resulting in an increase in the bleeding time.[5]

Von Willebrand factor decreased more than might be expected from plasma dilution only. The mechanism by which gelatin interacts with vWF is not completely clear, vWF could attach to gelatins through its collagen binding sites, the low level of vWF observed in their *ex vivo* experiment being explained by a rapid clearance of the vWF-gelatin complexes.[6]

A novel medium Mw starch with a molar substitution ratio of 0.4 (Voluven, Fresenius, Bad Hambourg, Germany) has been introduced recently on the European market. This HES solution presents an *in vivo* Mw close to the ideal renal threshold, resulting in lower plasma and tissue accumulation. Therefore the formulation should have a lower impact on hemostasis and, in particular, on VIII/vWF complex and platelet aggregation, even after repetitive large dose infusion.[7]

Fluid compartment physiology and types of colloid fluids

Total body water for a 75-kg individual is approximately 45 L (60%). Two-thirds of this (30 L) is intracellular water. The remaining third (15 L) in the extracellular compartment is divided between the intravascular (3 L) and extravascular (12 L) compartments. The total intravascular volume (or blood volume) is approximately 5 L and has intracellular (red and white cells and platelets: 40% [2 L]) and extracellular (plasma: 60% [3 L]) components. Plasma is a solution in water of inorganic ions (predominantly sodium chloride), simple molecules such as urea, and larger organic molecules such as albumin and the globulins. [(8)]

The cell wall separates the intracellular compartment from the extracellular compartment. The capillary endothelium and the walls of arteries and veins divide the extracellular compartment into the intravascular and the interstitial (tissue or extravascular) compartments. Water moves freely through cell and vessel walls and is distributed throughout all these compartments. The energy-dependent Na^+/K^+ adenosine triphosphatase in cell walls extrudes Na^+ and Cl^- and maintains a sodium gradient across the cell membrane: Na^+ is an extracellular ion. The capillary endothelium is freely permeable to small ions such as Na^+ and Cl^- but is relatively impermeable to larger molecules such as albumin and the semisynthetic colloids, e.g., gelatins and starches, which are therefore normally theoretically maintained in the intravascular space.[(8)]

A solute in a solution generates an osmotic pressure that is proportional to the number of molecules or ions of solute and their charge characteristics: osmotic pressure is independent of solute molecular size. Osmotic pressure is generated only across semipermeable membranes, e.g., capillary endothelium and cell wall. Water is "pulled" along osmotic gradients toward the larger concentration of solutes to maintain isotonicity in all compartments: solute distribution determines the water content of each compartment and is in turn determined by the properties of the membranes separating the compartments. Solutes that can pass freely across a semipermeable membrane do not generate any osmotic pressure .[8]

The volume of distribution of infused fluids is therefore dictated by their solute content. In turn, the Plasma volume expansion(PVE) effect is directly related to the volume of distribution:

$$\text{Plasma volume expansion} = \frac{\text{Volume infused}}{\text{Volume of distribution}}$$

Assuming a closed model, infusion of water will expand all compartments in proportion to their total volume. Only 7% (intravascular fluid volume/total body water =3 L/45 L) of the infused water would therefore remain in the intravascular space. However, infusion of water is an irritant to veins because of its hypotonicity. Infusion of isotonic glucose solution (5% glucose) is rapidly equivalent to infusion of water, because the glucose is rapidly metabolized, leaving water, which behaves as described above. Infusion of isotonic crystalloid

(e.g., 0.9% NaCl or lactated Ringer's solution) will expand all the components of the extravascular volume, and 20% of the volume infused will remain in the intravascular space. Infusion of an "ideal colloid," containing large molecules that do not escape from the circulation, will expand the intravascular volume by 100% of the volume infused. *(9)*

Routine Intraoperative Fluid Administration

The goals of intraoperative fluid administration are to maintain:

1- Adequate oxygen delivery.

2- Normal electrolyte concentrations.

3- Normoglycemia.

The total fluid requirement is composed of compensatory intravascular volume expansion (CVE), deficit replacement, maintenance fluids, restoration of losses, and substitution for fluid redistribution (i.e., third space fluids):

Rate of fluid administration = CVE + Deficit + Maintenance + Loss + 3rd space. *(10)*

1-Compensatory Intravascular Volume Expansion

Intravascular volume usually must be supplemented to compensate for the venodilation and cardiac depression caused by anesthesia.