

LIPID EMULSION THERAPY



“God Speed”, oil on canvas, 1900, Edmund Blair Leighton

“The light of the world has passed away”, Pope Callixtus III, on hearing of the death of the White Knight, John Hunyadi in 1456.

From a humble, or at least a doubtful, origin the merit of John Hunyadi promoted him to the command of the Hungarian armies. His father was a Wallachian, his mother a Greek: her unknown race might possibly ascend to the emperors of Constantinople, and the claims of the Wallachians, with the surname of Corvinus, from the place of his nativity, might suggest a thin pretence for mingling his blood with the Patricians of ancient Rome. In youth he served in the wars of Italy, and was retained with twelve horsemen, by the bishop of Zagreb; the valour of the "White Knight", was soon conspicuous; he increased his fortunes by a noble and wealthy marriage and in the defence of the Hungarian borders, he won in the same year three battles against the Turks. By his influence Ladislaus of Poland obtained the crown of Hungary; and the important service was rewarded by the title and office of Waivod of Transylvania...During the absence and minority of Ladislaus of Austria, the titular king Hunyadi was elected supreme captain and governor of Hungary; and if envy at first was silenced by terror, a reign of twelve years supposes the arts of policy as well as of war. Yet the idea of a consummate general is not delineated in his campaigns, the white knight fought with the hand rather than the head, as the chief of desultory barbarians, who attack without fear and fly without shame, and his military life is composed of a romantic alternative of victories and escapes. By the Turks who employed his name to frighten their perverse children, he was corruptly denominated Jancus Lain, or the Wicked, their hatred is the proof of their esteem; the kingdom which he guarded was inaccessible to their arms; and they felt him most daring and formidable when they fondly believed the captain and his country irrevocably lost. Instead of confining himself to a defensive war, four years after the defeat of Varna, he again penetrated into the heart of Bulgaria, and in the plain of Cossova, sustained, till the third day the shock of the Ottoman army, four times more numerous than his own. As he fled alone through the woods of Wallachia, the hero was surprised by two robbers, but while they disputed a gold chain that hung at his neck, he recovered his sword, slew the one, terrified the other, and after new perils of captivity, or death, consoled by his presence an afflicted Kingdom. But the last and most glorious action of his life was the defence of Belgrade against the powers of Mehmet the Second in person. After a siege of forty days the Turks, who had already entered the town, were compelled to retreat; and the joyful nations celebrated Hunyadi and Belgrade as the bulwarks of Christendom. About a month after this great deliverance the champion expired; and his most splendid epitaph is the regret of the Ottoman prince; who sighed that he could no longer hope for revenge against the single antagonist who had triumphed over his arms. On the first vacancy of the throne Matthias Corvinus, a youth of eighteen years of age was elected and crowned by the grateful Hungarians. His reign was prosperous and long: Matthias aspired to the glory of a conqueror and a saint; but his purest merit is the encouragement of learning and the Latin orators and historians, who were invited from Italy by the son, have shed the lustre of their eloquence on the father's character.

Edward Gibbon, "The History of the Decline and Fall of the Roman Empire", volume 6, 1787.

In May of 1453, all Europe stood astonished and horrified at the news that Constantinople had fallen to the Turk. Not since the sack of Rome in 410 AD had such calamity struck the seemingly eternal "Roman" empire, and this time the calamity was terminal. In truth of course the Roman Empire had long ceased to exist, in reality collapsing in 476 AD. In the East the empire survived but over the centuries it had evolved into a purely Greek entity, known as the Byzantine Empire, that bore little

resemblance to the Rome of the early Fifth century A.D. Rather it was the legitimate successor of the Roman empire but by 1453 this legacy was only the faintest of shadows of the former Greco-Roman world - an anachronism that had long outlived its real world relevance. Only the city of Constantine remained and this also, the very palest shadow of its former grandeur. The "empire" however, such as it was in 1453, had existed for longer than anyone could guess, its true relevance lying in the symbolic but immensely prestigious vestige of a long and glorious past. To the medieval mind, the city of Constantine seemed as fixed and eternal as the very Earth itself or the stars in the sky. So when the inevitable end came, the shock was more cultural than anything truly unexpected. Be that as it may, the new Ottoman threat was very real, and it was the fall of Constantine's city which really crystallized for the West the imminent danger their culture and heritage now faced, a threat which had in reality existed for at least half a century. The fate of the city had previously been saved by the terrifying Mongols, who appeared as if from nowhere to defeat the Turkish Sultan Bayezit I on the eve of his attack on the city in 1402, the date at which, were it not for these hellish hordes, would today be remembered as the final collapse of the old Greco-Roman world.

In 1453, Mehmet II having finally taken Constantinople, stood at the very gates of Europe, poised to invade its hinterland. This was a pivotal moment in Western civilization. Such moments had occurred on a few occasions in the past, but each time a champion had appeared to heroically hold off the enemy at the gate. Leonidas, Aetius, Charles Martel and the enigmatic Callinicus, had been these champions. Pope Callixtus III, trembling in Rome, called out for a new champion to save the West from the wrath of the Turks, led by the all conquering Mehmet II and his immense army. And as history records, a champion did emerge - not from France, or from England or from the Italian states, or from the Habsburg lands - it came from a most unexpected place - the kingdom of Hungary, under the leadership of the legendary John Hunyadi the original "White Knight in Shining Armor", so named for his distinctive highly polished gleaming suite of amour instantly recognized on the battlefield by Hungarian and Turk alike. Hunyadi had been fighting a bitter guerilla type warfare against the Ottomans for many years, striking in ambush when they were most vulnerable inflicting terrible damage and then dissolving away into the impenetrable forests of Transylvania whenever outnumbered or out maneuvered, frustrating the Turks in their frenzied pursuit of him. On July 4th 1456, Mehmet II launched 100,000 soldiers in an all or nothing assault against the Hungarian heartland - Belgrade. It seemed inevitable that Belgrade would suffer the same horrific fate as Constantinople, and if Belgrade fell, the way to Callixtus' Rome itself lay open. Hunyadi with the aid of an extraordinary Franciscan friar, by the name of Giovanni da Capistrano, whose hellfire oratory recruited huge numbers of the Hungarian and Romanian peasantry, rode to the defense of Belgrade and took personal command of the siege. The battle was brief and incredibly intense, but Hunyadi standing on the battlements in his shining armor was enough inspiration to hold off the Turkish attack. In a brilliant counter-stroke Hunyadi unexpectedly took the attack outside the walls and ambushed the main Turkish camp. Mehmet had had enough. He left for Constantinople, and Christendom had been saved. For the next three generations Hungary would be free of the Turks, until, 70 years later when the greatest of all the Sultans, Suleiman the Magnificent would finally take the city with a force twice the size of Mehmet's. By that time however the rise in Habsburg and Polish power would be enough to once again hold off the Ottoman threat at Vienna. Hunyadi had saved the West at a time when no other power could stand up to the Ottomans. Just a month after the siege of Belgrade John

Hunyadi died of the plague. Pope Callixtus III, on hearing of the death of the White Knight, sadly exclaimed - “The light of the world has passed away”.

Today John Hunyadi is remembered as a national hero not only to Hungary, and Romania, where he fought many of his battles, but also to the West in general as the White Knight in shining armour who saved European civilization. When we are faced with the desperate situation of cardiovascular collapse in cases of local anaesthetic toxicity, we may need the assistance of a “White Knight” - this white knight will come to us in the form of a “lipid rescue”.



“Titusz Dugovics Sacrifices Himself for Hungary”, oil on canvas, 1859, Sandor Wagner

The Hungarian hero Titusz Dugovics, fighting in the army of John Hunyadi, grabs an Ottoman Commander and hurls both himself and the Turk over the parapets, during the Siege of Belgrade, 1456. Behind him the Hungarian flag is being raised on the battlements.

LIPID EMULSION THERAPY



Intralipid is a milky white emulsion of soya bean oil in water, (similar in appearance to propofol).

Introduction

Lipid Emulsion Therapy (or intravenous lipid emulsion or **IVLE** therapy or “lipid rescue”) is a newer antidote that is still under investigation.

It may have a role in the treatment of patients with arrhythmias and cardiovascular collapse caused by **local anaesthetic agents**.

This role may further extend to other lipophilic agents.

Preparation

Intravenous lipid emulsion is a sterile emulsion of soya bean oil in water, that is normally used in parenteral nutrition.

Bottles:

- Intravenous lipid emulsion 20 % in 100 mls
- Intravenous lipid emulsion 20 % in 500 mls

Mechanism of action

There are a number of theories on how this agent is beneficial.

The most popular current theory is that the emulsion creates an intravascular lipid phase in the blood stream which is then able to extract lipid soluble drugs from their tissue binding sites, (via sequestration or partitioning).

There are however several alternative theories, involving augmented myocardial fatty acid utilization or direct effects on ion channels.

Indications

Indications include:

First Line Therapy:

1. Local anaesthetic induced cardiovascular collapse, resistant to standard ALS procedures.

Second line therapy:

Consider in the arrested or pre-arrested patient:

2. Rescue therapy for refractory cardiac arrest caused by other **highly lipophilic** (lipid soluble) drugs.

Lipid soluble drugs for which lipid rescue could be considered include:

- Tricyclic antidepressants.
- Propranolol
- Verapamil

Adverse reactions

These may include:

1. Allergic or anaphylactic reactions
2. Pulmonary hypertension and acute lung injury have been described, however whether this is due to the underlying toxicological problem or the lipid emulsion is uncertain.
3. Pancreatitis.

Dosing

Optimal dosing regimens are uncertain.

The following has been used: ¹

Bolus:

- **IV bolus over 1 minute of 1-1.5 mls/ kg of 20 % solution of lipid emulsion.**
- **This same bolus dose can be repeated once or twice at 3-5 minute intervals as required.**

Following this an infusion may be commenced until therapeutic end point is reached:

Infusion:

0.25 ml/kg per minute (i.e 15 mls/kg /hr) until therapeutic end point is achieved.

This may be increased to **0.5 ml/ kg per minute** ((i.e around 30 mls/kg/hr) for persisting hypotension.

Alternatively for an average 70 kg adult:

Using a 20 % solution of IVLE give a bolus of 100 mls over 1 minute.

Follow with an infusion of: 400 mls over 20 minutes

If still no response give further bolus doses, increase infusion rate to 400 mls over 10 minutes and persist with other usual life support protocols as required.

Therapeutic end-points

- A return of spontaneous circulation
- Stabilization of hemodynamic parameters (resolution of arrhythmias/ hypotension)

References

1. Intravenous Lipid Emulsion in L Murray et al. Toxicology Handbook 3rd ed 2015.
2. Grant Cave, Martyn Harvey, Andis Gaudins: Intravenous lipid emulsion as antidote: A summary of published human experience. EMA, (2011) 23, 123-141.

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