Kopalasuntharam Muhunthan was born in Jaffna and had his primary education at St. Peter's College - Colombo and Secondary education at Royal College - Colombo and St John's College - Jaffna.

He entered the Faculty of Medicine, University of Jaffna during the IPKF occupation and continued his education during the height of conflicts prevailed at that time. He graduated with honors in 1997 from University of Jaffna.

Pursued in the field of Obstetrics and Gynaecology with the Postgraduate Institute of Medicine and after obtaining his MS in Obstetrics and Gynaecology he proceeded to the United Kingdom to train at Norfolk and Norwich University Hospital and James Paget Hospital of the Cambridge deanery. During this period, he was admitted as member of the Royal College of Obstetricians and Gynaecologists by training and examination and presently is a Fellow of the Royal College of Obstetricians and Gynaecologists.

He was Board Certified as a Specialist in Obstetrics and Gynaecology in 2003 and had worked as a consultant in the Eastern and North Western provinces for eight years. In 2011 he joined the Department of Obstetrics and Gynaecology as a Senior Lecturer. In addition to his undergraduate teaching commitments he is actively involved in postgraduate education with the PGIM and has served at varied capacities including being appointed as the chief-examiner for the selection MD examination in Obstetrics and Gynaecology.

He has several peer reviewed publications and has authored eight chapters in books published by renowned international scientific publishers. His current research interests are maternal medicine, intrapartum fetal monitoring, gynecological cancer screen and obstetric haemorrhage

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Jaffna Medical Association

Professor. C. Sivagnanasundram Oration 2020

Tranexamic Acid - Revival of an Old Drug to Save Mothers' Lives

By

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MBBS (SL), MS (Obs & Gyn), FRCOG (UK)
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Message from the President of Jaffna Medical Association

It is a great pleasure and honor for me to welcome you all, to this memorial oration of our late Professor. C. Sivagnanasundram.

Professor. C. Sivagnanasundaram, Emeritus Professor of Community Medicine, University of Jaffna, was a valuable medical professional, an academic, a teacher, a researcher and above all a kind and considerate human being. He provided these services with great dedication and commitment for many years. His interest and contribution to the health research earned him personal satisfaction as well as recognition from his peers and students not only in Sri Lanka but also internationally.

Oration of the Annual Academic Sessions of the Jaffna Medical Association is a formal scholarly presentation made by an academic, based on his/her scholarly work.

This year, the Professor. C. Sivagnanasundram memorial oration is delivered by Dr Kopalasuntharam Muhunthan, Consultant Obstetrician & Gynaecologist and Senior Lecturer at Faculty of Medicine, University of Jaffna. He is a man of diverse capabilities. His excellence as a teacher and his commitment to the medical profession, made him as an outstanding member of our profession.

His oration “Tranexamic acid - revival of an old drug to save mothers' lives" is very relevant to this year’s theme of the Annual Scientific Sessions of Jaffna Medical Association “Health Challenges Beyond 2020-educate and engage”.

Thank you

Dr. S. K. Arulmoi

Preamble

Professor. C. Sivagnanasundram affectionately known as “Nanthi” was an eminent academic, writer, community physician, great teacher and above all a person with humane touch.

He obtained the degree from the University of Ceylon in 1955 and served in the state health services for several years. In 1965 he joined the Department of Preventive and Social Medicine at the Faculty of Medicine, University of Ceylon, Peradeniya.

In 1968, he obtained the DPH (London) and was awarded the PhD by the University of London in 1971. He was conferred an honorary DSC by the University of Jaffna in 1995.

In 1978, Professor Sivagnanasundram moved to the newly established Faculty of Medicine at the University of Jaffna as a founder Professor of Community Medicine and held this post until his retirement. He continued to serve in this capacity for 12 years even after formally retiring from the university service.

His contributions to the Faculty of Medicine were wide and varied and were not limited to medical profession. His book “Learning Research” has had two editions and is widely used by both medical undergraduates and postgraduates.

His talents go well beyond his academic contributions. He has written many novels and short stories and many of his novels have received Sri Lanka Shakithya academy awards.

I was fortunate to be his student and always cherish the memories of his stern but affectionate personality. I sincerely hope that my oration in his name will do justice to Professor. C. Sivagnanasundram’s ideologies.

Tranexamic acid – Revival of an old drug to save mothers lives

Background

Maternal mortality is one of the dreaded events in the field of medicine where a woman loses her life directly or indirectly as result of a pregnancy though it is considered a physiological process.

Almost all the countries in the world, health organizations, professional bodies, researchers and individuals who are involved in the care of pregnant women are constantly working to reduce maternal mortality at different levels.

Unprecedented numbers of researches are being conducted around the world in a quest to search for a solution in terms new management strategies, drugs, devices and surgical techniques to save mothers from dying due to a complication of pregnancy.

Recently an old drug called tranexamic acid (TXA) has been shown to be effective in the treatment of postpartum hemorrhage, which still is a leading cause of maternal mortality worldwide.

The following excerpts I hope will shed light on this almost forgotten drug which has revived itself to save mothers lives, after half a century of its intended invention.

Early history of tranexamic acid

It all started with a Japanese ‘wife and husband’ team in Tokyo in the 1950s, the husband Shosuke Okamoto and the wife Utako Okamoto.

Fig. 1. Shosuke Okamoto and Utako Okamoto

At that time Shosuke Okamoto was an associate professor in physiology at Kobe University and Utako Okamoto was a senior lecturer in physiology at Keio University School of Medicine.

In the 1950s the medical field was heavily male-dominated and Utako had to work twice as hard and long for the chance to even be acknowledged for her accomplishments. It was said that she had to bring her child into the laboratory because the system did not support working mothers.[1]

Fig. 2. Shosuke and Utako working in the laboratory in 1960

Japan was recovering from the heavy scars of second world war and resources were hard to find at that time, especially for something like blood research.

Yet this couple were determined to identify a drug that could reduce bleeding during and after childbirth. The couple were morally inclined towards this venture because during this period globally as well as in Japan postpartum hemorrhage was the leading cause for maternal deaths, killing almost every 50th mother who delivered a baby.

They knew that there were already substrates in the blood that broke down clots and were researching to find a drug to stop or slow the breakdown of blood clots if possible. The amino acid lysine was found to have some effect but they kept looking for a more potent drug.

Their hard work paid off and in 1962 they published a paper about a new drug called Amino-Methyl-Cyclohexane-Carboxylic-Acid (AMCHA) currently known as tranexamic acid (TXA) in the Keio Journal of Medicine. Their newly discovered drug was said to be 27 times more potent than a previous lysine-based substance.[2]

Contrary to the fact that many of the hemostatic and anti-coagulant drugs were discovered by serendipity, tranexamic acid was discovered by this couple with a purpose, that is to save mothers dying from postpartum hemorrhage.

Though this couple invented this drug to save mothers lives, the local obstetricians were not too interested in using it and this new drug was almost forgotten. No research or trials followed this invention and the drug was virtually *orphaned* by the pharmaceutical industry.

An orphan drug is a pharmaceutical agent developed to treat medical conditions which, because they are so rare, would not be profitable to produce without government assistance.[3]

Interestingly in certain countries there exist a pharmaceutical law called ‘orphan drugs law/act’ which ensures that at least one manufacturer is forced to continue production of these sparsely used drugs.

By the late 1990s, intravenous tranexamic acid was only occasionally used and there was just one manufacturer who produced it under an ‘orphan drugs’ law.

Mode of action of tranexamic acid

It's very important to recapitulate the human hemostatic pathway to understand the mode of action of tranexamic acid.
Hemostasis is the physiological process that stops bleeding at the site of an injury while maintaining normal blood flow elsewhere in the circulation.

The endothelium in blood vessels maintains an anticoagulant surface that serves to maintain blood in its fluid state, but if the blood vessel is damaged components of the subendothelial matrix are exposed to the blood.
Several of these components activate the two main processes of hemostasis to initiate formation of a blood clot, composed primarily of platelets and fibrin. This process is tightly regulated such that it is activated within seconds of an injury and remain localized to the site of injury. Followed by this process the blood loss is stopped by formation of a hemostatic plug.

There are two main components to hemostasis and primary hemostasis refers to platelet aggregation and platelet plug formation where platelets are activated in a multifaceted process, and as a result they adhere to the site of injury and to each other, plugging the injury.

Secondary hemostasis refers to the deposition of insoluble fibrin, which is generated by the proteolytic coagulation cascade. This insoluble fibrin forms a mesh that is incorporated into and around the platelet plug.

This mesh serves to strengthen and stabilize the blood clot. These two processes happen simultaneously and are mechanistically intertwined.

The opposite of this is fibrinolysis which is a key component of the hemostatic processes that maintain patency of the vascular system.

Circulating plasminogen is converted to the serine protease plasmin by the enzyme tissue plasminogen activator (tPA), causing the breakdown of fibrin to fibrin degradation products (FDPs).

Multiple anticoagulant mechanisms regulate and control these systems to maintain blood fluidity in the absence of injury and generate a clot that is proportional to the injury. The proper balance between procoagulant systems and anticoagulant systems is critical for proper hemostasis and the avoidance of pathological bleeding or thrombosis (Fig 1).

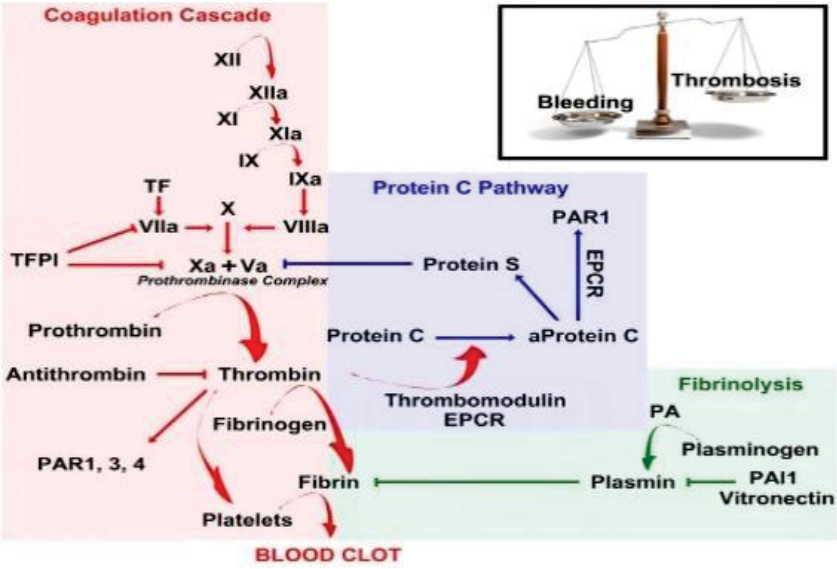

Fig. 3. The human hemostatic pathway

Tranexamic acid which is a synthetic derivative of the amino acid lysine (Fig. 4) acts in the fibrinolytic side of this complex system by binding to the 5-lysine binding sites on plasminogen (Fig. 5).

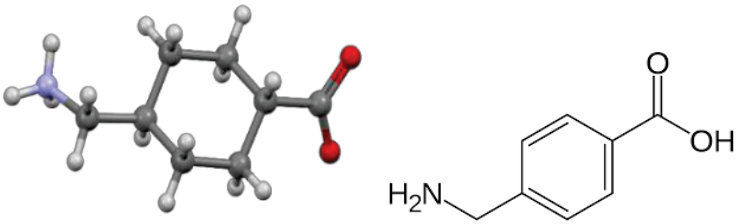

Fig. 4. The chemical structure of Tranexamic acid

This binding inhibits the formation of plasmin and displaces plasminogen from the fibrin surface. This prevents the fibrin from breaking down to fibrin degradation products.[4]

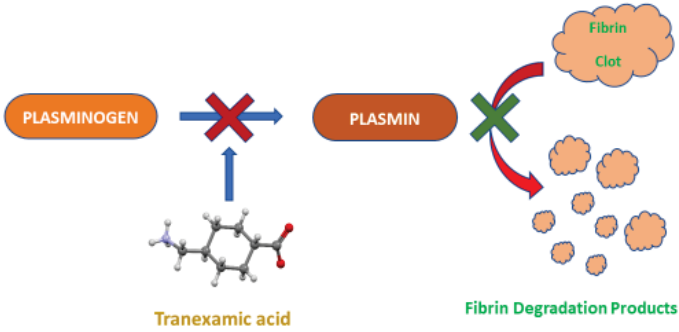

Fig. 5. Action of Tranexamic acid

Tranexamic acid is minimally bound to plasma proteins (3%) and there is no apparent binding to albumin.

Less than 5% of tranexamic acid is metabolized in the body and the rest is eliminated by urinary excretion primarily via glomerular filtration.

Though the pharmacokinetics of this in adults are well documented after intravenous and oral administration, robust data are not available for postpartum women.

Pregnancy results in marked physiological changes in the vascular, circulatory, haemostatic and renal systems and the pharmacokinetic values of non-pregnant adults cannot be readily adopted to pregnant and postpartum women.

Initial Recognition of Tranexamic Acid

Though there were some initial interest in late 1960s in using tranexamic acid for heavy menstrual bleeding it was not approved for this purpose at that time.

Later during 1980s its oral preparation which was called the 'novel oral formulation' was slowly becoming popular as a treatment option for heavy menstrual bleeding with more randomized controlled trial being conducted and published during this time.

When its effectiveness was becoming more evident the food and drug administration (FDA) first approved tranexamic acid for the treatment of heavy menstrual bleeding in 2009.

With growing popularity of its use in heavy menstrual bleeding the *Cochrane Database* in 2018 published its systematic review on the use of tranexamic acid for the treatment of heavy menstrual bleeding. This systematic review included 13 randomized controlled trial with 1312 participants.[6]

The Cochrane systematic review concluded that:

- Antifibrinolytic treatment (TXA) appears effective for treating HMB compared to placebo and herbal remedies.
- Antifibrinolytic treatment (TXA) appears effective for treating HMB compared NSAIDs.
- Antifibrinolytic treatment (TXA) appears effective for treating HMB compared oral luteal progestogens.
- Antifibrinolytic treatment (TXA) appears to be less effective than (levonorgestrel intrauterine system) LIUS for treating HMB.

Emerging Concerns of Thrombosis

With more evidence emerging about the effectiveness of tranexamic acid, there were rising concerns as to whether it increases the risk of thrombosis in these patients.

This concern was mainly based on its mode of action namely preventing a fibrin clot or a thrombus at a site of injury from being dissolved by plasmin.

The study group of the Cochrane systematic review which looked at its usefulness in the treatment of heavy menstrual bleeding was also concerned about this potential but serious side effect and they too did look in to this complication.

Cochrane systematic review reported that most studies did not include venous thromboembolism (VTE) as an end-point but studies that did measure VTE have not shown any increase in risk with antifibrinolytic treatment for heavy menstrual bleeding.[6]

Observational, population-based studies on the association between use of tranexamic acid for menorrhagia and VTE showed a negative association between tranexamic acid and VTE.[7]

The thrombogenic risk of tranexamic acid has been extensively researched during its uses in cardiac and orthopedic surgeries. Current evidence suggests that when used after excluding the contraindications with appropriate post-operative precautions there was no increase in the frequency of thrombosis compared to the control groups.[8]

The use of tranexamic acid in hemorrhage due to trauma

Over the last decade tranexamic acid was slowly becoming popular with cardiac and orthopedic surgical procedures to reduce intra and post-operative bleeding.

Many clinical practice guidelines presently recommend the intraoperative use of tranexamic acid in cardiac and orthopedic procedures and its benefits are well established as an antifibrinolytic with proven efficacy.

But surprisingly it was never routinely used in major trauma patients even though hemorrhage was known to be the leading cause of death among these patients from primary injury to organs and blood vessels.

A 'coffee time' conversation between an emergency physician and an anaesthetist, both of whom had recently been working in cardiac surgery, led to the question about the routine use of an antifibrinolytic in trauma.[9]

With the involvement of a much larger group of researchers, this resulted in the CRASH-2 trial in 2005 which stands for **C**linical **R**andomisation of an **A**ntifibrinolytic in **S**ignificant **H**aemorrhage - 2.

The CRASH-2 trial

This was a large, multicenter, randomised, double-blind, placebo-controlled trial and was undertaken by the Clinical Trials Unit of the London School of Hygiene and Tropical Medicine in 2005. Worldwide 40 countries and 274 hospitals participated in this trial with a study population of 20,211.

Adult trauma patients with significant haemorrhage (systolic blood pressure <90 mm Hg or heart rate >110 beats per min, or both), or who were considered to be at risk of significant haemorrhage, and who were within 8 hours of injury, were eligible for the trial.

Enrolment began in May 2005 and patients were randomized to double-blinded treatment with either tranexamic acid or a matching placebo, given within 8 hours of presentation.

All analyses were done on an intention-to-treat basis and followed up to 4 weeks with endpoint of the study being death in-hospital within 4 weeks of injury.[10]

After eligibility had been confirmed patients were randomly allocated to receive a loading dose of 1 g of tranexamic acid infused over 10 min, followed by an intravenous infusion of 1 g over 8 h, or a matching placebo (0·9% saline). In addition, all the patients received appropriate care according to the type of trauma they sustained.

Endpoint of the study being death in-hospital within 4 weeks of injury Fig. 6 shows the causes of deaths among the trial participants of the CRASH-2.

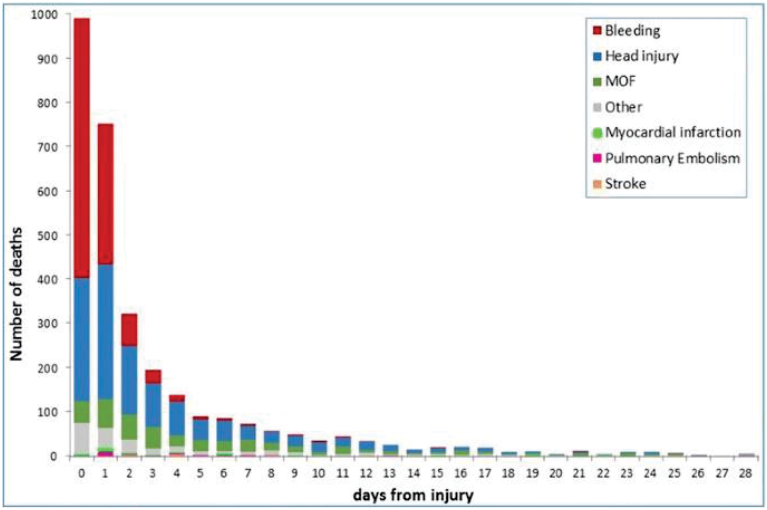

Fig. 6. Causes of deaths among the adult trauma patients against the time from injury or trauma amongst the CRASH 2 trial participants.

The results of the CRASH-2 trial were published in the Lancet in 2010. The trial concluded that the early administration of tranexamic acid to trauma patients with, or at risk of, significant bleeding reduces the risk of death from haemorrhage. The trial also stated that:

- There was no apparent increase in fatal or non-fatal vascular occlusive events.
- All-cause of mortality was significantly reduced with tranexamic acid.
- TXA appears most effective when given early after the trauma and should be given within approximately 3 hours.
- Treatment beyond 3 hours of injury was shown to be ineffective.

Worldwide trend of maternal mortality and postpartum hemorrhage

The maternal mortality ratio (MMR) is defined as the number of maternal deaths per 100,000 live births during a given time period.

Though the maternal mortality ratio has drastically dropped worldwide over the last six decades, WHO in a recent statement mentioned that the 'Maternal deaths declines slowly with vast inequalities worldwide'.[11]

Several countries in the world have managed to keep the maternal mortality ratio as a single digit and Fig. 7 shows the latest available maternal mortality ratios of some selected countries with highest and lowest in the world. Fig. 8 shows how these countries are segregated in the world.

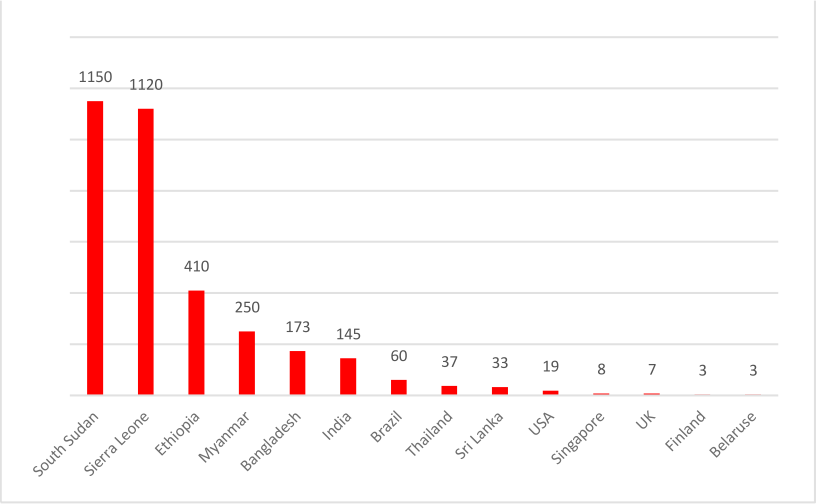

Fig. 7. Maternal mortality ratios of some selected countries in 2017

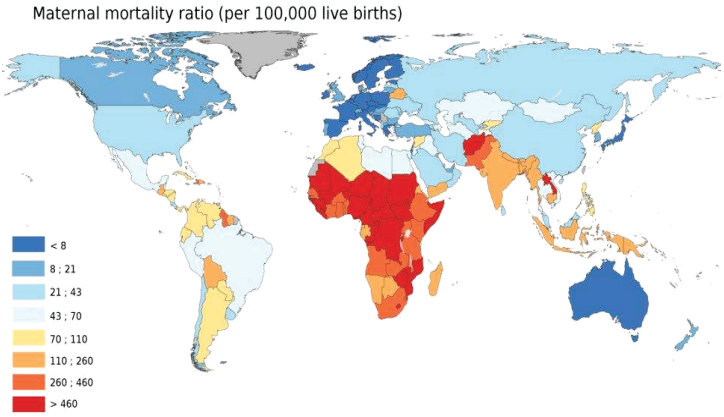

Fig. 8. worldwide trend of Maternal mortality ratios

The most recent information on maternal mortality statistics by the WHO has comprehensively analyzed the data up 2017 and according to their statement:[12]

- Between 2000 and 2017, the maternal mortality ratio dropped by about 38% worldwide.
- Every day in 2017, approximately 810 women died from preventable causes related to pregnancy and childbirth.
- 94% of all maternal deaths occur in low and lower middle-income countries.
- Young adolescents (ages 10-14) face a higher risk of complications and death as a result of pregnancy than other women.
- Skilled care before, during and after childbirth can save the lives of women and newborns.

Fig. 9 shows how the maternal mortality ratio has dropped in Sri Lanka over the last century and this trend is somewhat similar to several countries in the world.[13]

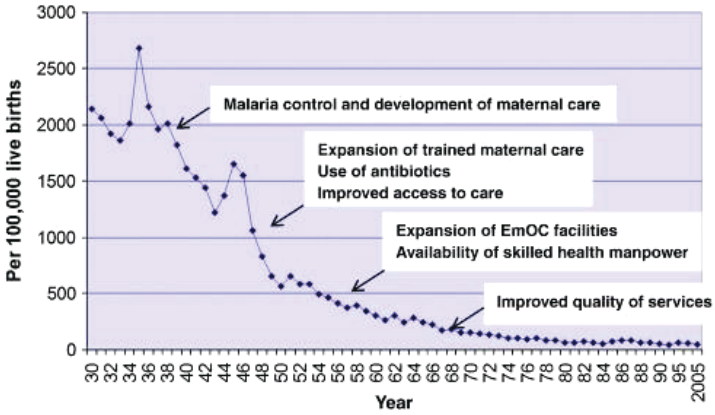

Fig. 9. Trend of maternal mortality ratio in Sri Lanka over the last century.

The sharp declines in the 1940s, 50s, 60s and 70s are attributable to factors like control of malaria in Sri Lanka, use of antibiotics, improved health manpower and overall improvement of services.

Significant improvement in health care, economies and new inventions in terms of drugs, devices and surgical techniques have surely contributed to this exponential drop in MMR worldwide as well as in Sri Lanka.

Sri Lanka is said to fare well among the South Asian countries and Fig. 10 compares our position among the South Asian Association for Regional Cooperation (SARRC) countries.

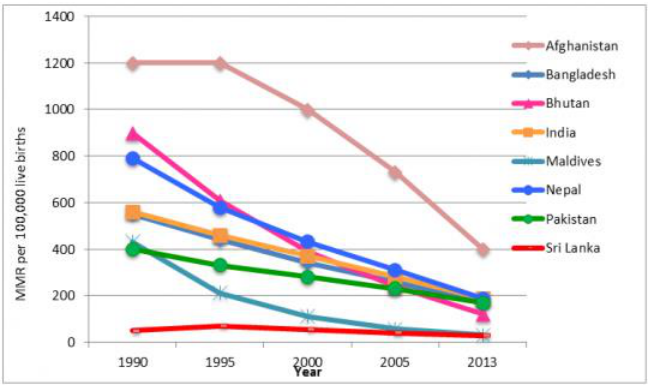

Fig. 10. Maternal mortality ratios compared among the SARRC countries.

Though we fare best among the regional countries our latest published MMR was 32 per 100,100 live births (2018).

In Sri Lanka still more than 100 mothers die every year and throughout the history we have not been able to reduce absolute number of deaths to less than 100. Fig. 11 shows the absolute number of maternal deaths over the last two decades.[13]

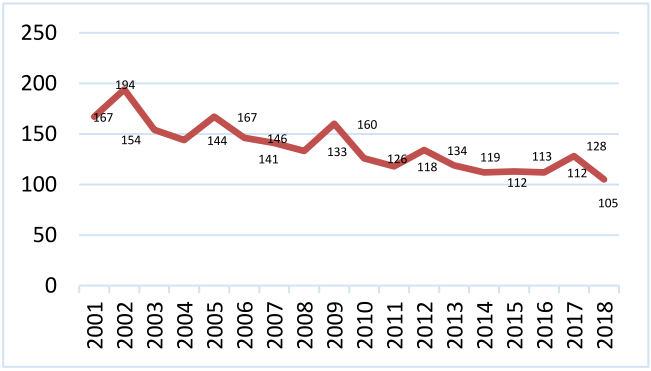

Fig. 11. Absolute number of maternal deaths each year in Sri Lanka

The contribution of primary postpartum hemorrhage to maternal mortality in Sri Lanka

Primary post-partum haemorrhage, usually defined as a blood loss of more than 500 mL within 24 h of giving birth.

It affects about 5% of all women giving birth around the world and is the leading single cause for maternal death worldwide, responsible for about 100,000 deaths every year.[14]

Most of the deaths due to postpartum haemorrhage occur soon after giving birth and (99%) occur in low-income and middle-income countries with poor access to health care facilities.[14]

The cause specific MMR in Sri Lanka from 2001-2017 is shown in Fig. 12 and postpartum hemorrhage has been the leading cause almost throughout until 2017.

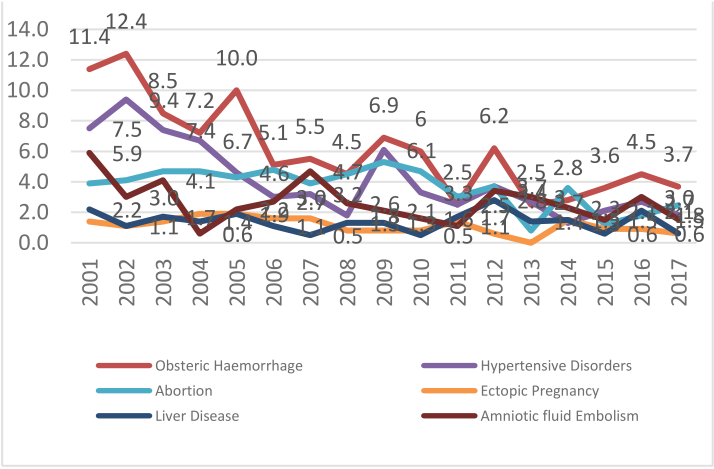

Fig. 12. Cause specific maternal mortality ratio in Sri Lanka (2001-2017)

Different strategies have been described for preventing postpartum hemorrhage, including active management of the third stage of labour.

Once the diagnosis of postpartum hemorrhage is established, the use of uterotonics including prostaglandins, intrauterine balloon tamponades, brace sutures of the uterus and occlusion of the feeding blood vessel either surgically or radiologically has been proven to be beneficial.

Though lack of facilities and substandard care are major contributors in low and middle-income countries, in other situations we have reached a stalemate with the postpartum hemorrhage and it appeared that we also have runout of treatment options.

Unsurprisingly following the publication of the CRASH-2 trial there were mounting interests to look at the usefulness of tranexamic acid in the management of hemorrhage. Until such time the use of antifibrinolytic agents have never been a component of the management strategies of postpartum hemorrhage.

After all tranexamic acid was originally invented by the Okamoto couple to save mothers dying from postpartum hemorrhage.

The WOMAN Trial

Again, the Clinical Trials Unit of the London School of Hygiene and Tropical Medicine took up this task called the WOMAN trial which stand for '**Wo**rld **Ma**ternal A**n**tifibrinolytic' Trial.

Clinical Question of this study was 'Does the early administration of tranexamic acid, compared with placebo, reduce death from bleeding in women with postpartum haemorrhage"

It was a large, multicenter, randomised, double-blind, placebo-controlled trial and recruited women aged 16 years and older with a clinical diagnosis of postpartum hemorrhage after a vaginal birth or caesarean section from 193 hospitals in 21 countries between March, 2010 and April, 2016.

20,060 women were enrolled and randomly assigned to receive either 1 g intravenous tranexamic acid administered intravenously over 10 minutes or a matching placebo in addition to standard care of their postpartum hemorrhage.

Baseline characteristics were very well balanced in this trial with regards to included age, type of delivery (71% vaginal; 29% caesarean section).

If bleeding continued after 30 min, or stopped and restarted within 24 h of the first dose, a second dose of 1 g of tranexamic acid or placebo was given.

All analyses were done on an intention-to-treat basis with endpoint of the study being death from post-partum hemorrhage.[15]

The results of this much awaited WOMAN trial were published in the Lancet in 2017.

The trial results concluded that:

- Death due to bleeding was significantly reduced in women given tranexamic acid especially in women given treatment within 3 hours of giving birth.
- All other causes of death did not differ significantly by group.
- Hysterectomy was not reduced in the tranexamic acid group
- The composite primary endpoint of death from all causes or hysterectomy was not reduced with tranexamic acid
- Adverse events (including thromboembolic events) did not differ significantly in the tranexamic acid versus placebo group.

While the WOMAN trial was in progress on the 21st of April 2016 the surviving inventor of tranexamic acid Utako Okamoto died at the age of 98. Not many scientists are honored by reputed medical journals on their death but the LANCET published her obituary.

WOMAN study collaborative group in their last concluding statement mentioned that:

'In the WOMAN trial, tranexamic acid was given by intravenous injection. However, in low-income and middle-income countries, many deaths from postpartum bleeding occur at home or settings where intravenous injections might not be feasible. Therefore, bioavailability of tranexamic acid after non-intravenous routes of administration needs to be assessed.'

At the same time in 2017 the WHO in its updated recommendation on tranexamic acid for the treatment of postpartum hemorrhage stated that "Use of tranexamic acid is only applicable to intravenous administration and the evaluation of potential harm and benefit of other routs of administration of tranexamic acid is a research priority".[16]

These statements were made with an optimism that if effective concentration of tranexamic acid is achievable by a simpler oral route it could be used in the remotest parts of the world to save women dying from postpartum hemorrhage. Also at this point of time there were no published bioavailability studies on tranexamic acid after non-intravenous routes of administration in postpartum women.

Interestingly when these statements were made in 2017 a group of researchers in Jaffna have already started a pharmacokinetic study to look at the bioavailability of tranexamic acid after oral administration in postpartum mothers.

The Jaffna Study

Our study was designed to investigate the pharmacokinetics of tranexamic acid after oral administration in postpartum women.

In the absence of any published data on the pharmacokinetics of tranexamic acid after oral administration in postpartum women, we considered this as the key step towards considering this route of administration to save mothers.

The research objectives were:

- To study whether an effective plasma concentration of tranexamic acid can be achieved after oral administration in postpartum mothers.
- And if yes, how fast this concentration could be reached and for how long this concentration would last.[17]

The study was conducted at the University Obstetric Unit, Teaching Hospital-Jaffna and the Department of Biochemistry, Faculty of Medicine, University of Jaffna.

As per *European Medicines Agency Committee* recommendation for bioequivalence studies, 12 healthy postpartum women with singleton pregnancies were recruited.[18]

Recruited participants were screened for contraindications to tranexamic acid: past and current history of intravascular clotting, hemorrhagic events, and procoagulant disorders. None of the pregnancies had been complicated by pregnancy-related medical disorders and patients with any preexisting comorbidities were excluded.

All participants underwent routine active management of the third stage, with intravenous oxytocin 10 international units after delivery, delayed cord clamping and controlled cord traction to deliver the placenta.

Blood loss was estimated by weighing swabs and blood collected in a waterproof drape on the labor ward.

One hour after delivery an arterial line was established by the anesthetist with an aim of obtaining frequent blood samples avoiding repeated venipunctures.

All study participants were administered the same preparation of 2 g of immediate release tranexamic acid orally with 50 mL of water, which corresponds in strength to 1g of intravenous tranexamic acid used to treat postpartum hemorrhage and they were monitored for 24 hours for adverse effects.

After administration of 2 g of tranexamic acid orally blood samples were collected over 12 hours namely at t 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours each amounting to only 1.8cc.

Samples were centrifuged at 2000g for 15 minutes at room temperature, and supernatants were stored at -70°C until analysis.

Plasma tranexamic acid concentration was determined by Shimadzu high-performance liquid chromatography (HPLC) using ortho-phthalaldehyde derivatization method at the Department of Biochemistry.

One of the obstacles of the analysis was the interference of the HPLC curve of tranexamic acid by the amino acid leucine which is present in blood. As a result, each sample had to be pretreated with leucine dehydrogenase before tranexamic acid concentration was determined by HPLC.

Samples for quality control were prepared with a known quantity of standard tranexamic acid added to analyte-free human plasma.

The accuracy of the assay method was between 97% and 99% and interestingly the standard tranexamic acid used for quality control was obtained from Japan. Fig. 13 represents a sample HPLC chromatogram obtained during the analysis at the Department of Biochemistry.

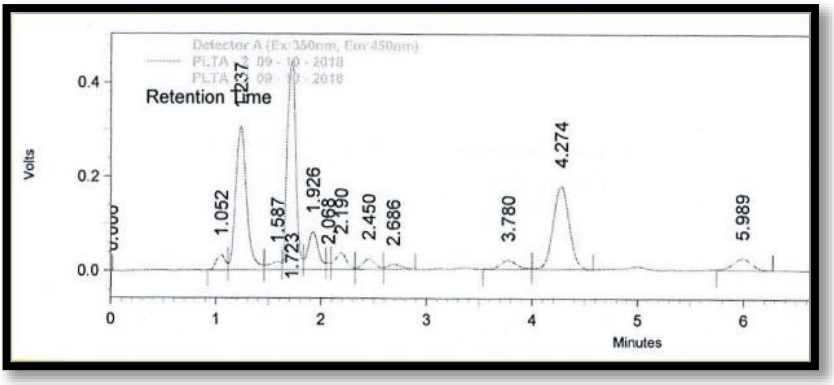

Fig. 13. HPLC chromatogram of Tranexamic Acid.

Results of our study.

Demographics of the 12 postpartum women who participated in the study is shown in Table. 1 and the Fig. 14 shows the plasma concentration of tranexamic acid in µg/ml versus time curve following single dose of 2 g of oral tranexamic acid in individual subjects.

Variables	Median	Range
Age (years)	28	24 - 33
Parity	2	1 - 2
Weight (kg) (measured at the onset of labour)	64	59 - 72
Height (cm)	158	150 - 165
BMI (kg/m2)	25.8	24.3 – 28.9
Estimated Blood Loss	230ml	170 - 300
Birth Weight (kg)	3.120	2.730 –3770

Table. 1. Demographics of the 12 postpartum women

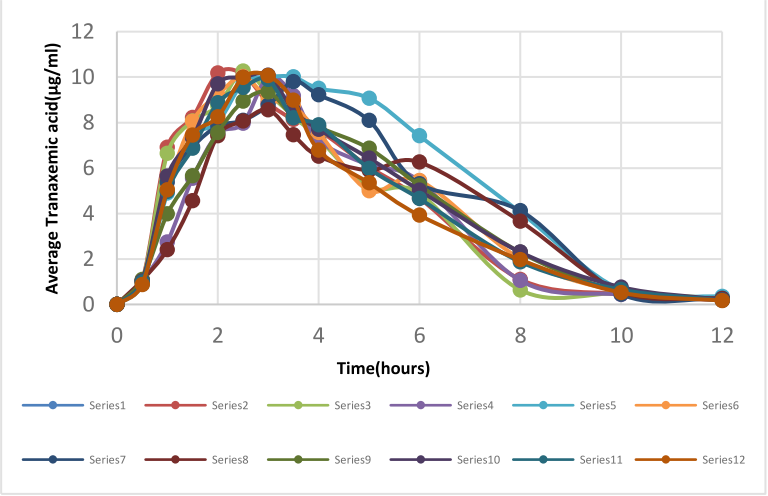

Fig. 14. Plasma concentration of tranexamic acid in µg/ml versus time curve following single dose of 2 grams of oral tranexamic acid in individual subjects.

Mean plasma concentration of tranexamic acid in micrograms/mL vs time curve after a single dose of 2 g of oral tranexamic acid in postpartum women is displayed in the Fig. 15 and the Table. 2 summarizes the pharmacokinetic values.

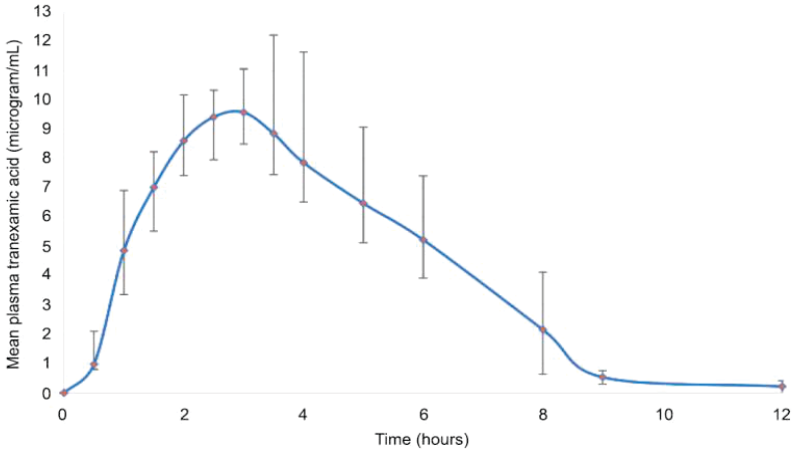

Fig. 15. Mean plasma concentration of tranexamic acid in micrograms/mL vs time curve after a single dose of 2 g of oral tranexamic acid in postpartum women.
Error bars represent the range.

Complex applied mathematical methods were required to calculate the required values from the above graph. Linear trapezoidal method was used to calculate the area under the curve for drug concentration. Geometric means were calculated to estimate the time pharmacologically effective drug concentrations were reached and the duration for which the pharmacologically effective concentrations lasted.

Elimination half-life for tranexamic acid was calculated as a parameter describing the linear terminal slope of the log concentrations.

Cmax range	10.06 ± 0.80 µg/dl 8.56 - 12.22 µg/ml
Tmax range	2.92 ± 0.34 hours 2.5 to 3.5 hours
AUC 0-12	49.16 µg.h/ml
$T_{1/2}$	1.65 hours
Time course of concentration ≥5µ/ml Initial Final Duration	 0.87 hours 6.73 hours 5.86 hours

Table 2: Pharmacokinetic Values. Cmax, maximum observed plasma concentration; Tmax, time to maximum plasma concentration; AUC0–12, area under the curve for drug concentration; T1/2, half-life.

Effective concentration of tranexamic acid needed to inhibit fibrinolysis has been quoted with wide variation in different studies.

In one of the most recent systematic review published by *Blood Coagulation & Fibrinolysis* a concentration of between 5–10 micrograms/mL was said to caused significant inhibition of Fibrinolysis and maximal inhibition was achieved between 10 and 15 micrograms/mL in adults. Also, at a concentration of 5 micrograms/mL, tranexamic acid has been shown to increase the

clot lysis time from 6 to 16 minutes.[19] Our results were interpreted based on the above values.

We concluded that within one hour of oral administration of tranexamic acid a minimum effective concentration of 5 micrograms/mL was achievable.

Also, this minimum effective concentration of 5 micrograms/mL lasted for almost 6 hours after a single oral administration.

The peak concentration of 10.06 micrograms/mL (Cmax) was reached by 2.92 hours (Tmax).

Our work being the first such pharmacokinetic study was published by The Journal of the American College of Obstetricians and Gynecologists in April 2020.

Conclusion

Though intravenous tranexamic acid has been shown to reduce the MMR due to all causes especially PPH, it has to be administered intravenously and also within 3 hours of delivery.

Millions of women who deliver their babies especially in poorer countries do not have access to intravenous tranexamic acid and are unlikely to get appropriate treatment in the foreseeable future.

In the absence of such facilities developing a cheap and easily administrable drug would save thousands of mothers as 99% of maternal deaths due to PPH occurs in these poor income countries.

In our study we were able to show that:

1. An effective tranexamic acid concentration capable of inhibiting fibrinolysis significantly is achievable following oral administration in postpartum women.
2. This effective tranexamic acid concentration is achievable within one hour of administration.
3. This effective tranexamic acid concentration also lasted for 6 hours

With the above key findings, we consider our study the stepping stone to explore the use of a less expensive, easily administrable oral tranexamic acid as an alternative option to intravenous preparation.

Though our initial results are promising we recommend further studies with larger sample sizes followed by randomised controlled trials to investigate the potential of oral tranexamic acid for the treatment or even prophylaxis of postpartum hemorrhage.

We foresee a day in future sooner rather than later where 2 g of oral tranexamic acid would be made available for women who deliver their babies at home and unsafe conditions to save their lives.

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