Review Article

Affordable Technologies to Stop Bleeding from Haemorrhage: New Role of Pharmacists in its R&D and Rational Use in Rural India

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ABSTRACT

This review focuses on developing biomedical first-aid (FA) technologies and its affordable rational use for the pre-hospital control of bleeding in external haemorrhage from limb extremities after traumatic injury. Public academic research hand in hand with government policies such as "Make-in-India" campaign could be explored for it. Pharmacists have unique skill set due to technological and clinical training in therapeutics. Subsequently, they can be given advanced training for the R&D and rational use of these haemostatic FAs for emergency care; particularly in rural areas of developing world. This may improve the accessibility and affordability of the medical technologies in the developing world.

Keywords: Haemorrhage, First aid, Point-of-Care, Pharmacist, Research, Education.

INTRODUCTION

In developed countries, care of haemorrhage in traumatic injury is achieved by a trauma care management team.[1] This team of intensive medical care personal includes neurologists, physiotherapist, psychological workers and nurse. As per the latest guidelines[2], the team provides evidence based recommendations, are suggested for acute management of trauma. This is to take care of the different tissue damage associated with poly-trauma by adopting suitable therapeutic/interventional techniques. However, such a detailed team is not affordable in developing world, particularly rural world. In this scenario life saving measures is most important, and in haemorrhage it is about "stopping the blood loss". Pre-hospital control of blood loss due to haemorrhage is successfully achieved using first-aids (FAs). However, such advanced technologies are underutilized in the rural world.

In the rural world, the usage of FAs is limited because; (1) it is unaffordable and less accessible and due to other (2) patient related factors. Another influencing factor is the patient related factors such as ignorance of treatment modalities as well as variations in clotting time of patients, affect acute care management of bleeding in trauma.[3] Thus, it is important to know, the principles of pre-hospital haemorrhage control; for the development of affordable FAs and its rational use.[4,5] One major scenario is in external bleeding from limb extremities, where FAs are very effective in stopping bleeding.[4,5] In this case, the essential principle, of stopping bleeding is that, (1) the pressure of blood flow to the open wound need to be reduced by appropriate techniques (using FAs such as tourniquets)[3-5], (2) clotting need to be induced at the wound site without affecting other tissues using FAs such as haemostatic dressings and elastic adhesives.[3,4] Subsequently, keeping the essential principles in mind, the technological vision about FAs for developing world can be (1) encouraging "indigenous technology development" to control the price of haemostatic FA technologies and (2) "decentralization of emergency care" by training pharmacists for the usage of such FAs.

This review provides a systematic approach to train pharmacists (with background in chemistry and biology) to participate in (1) R&D as well as (2) clinical practice of these advanced FAs for emergency care. Such research oriented programmes can be initiated in academia in universities as training programs. That can be translated into technologies with the help of industry to market. The biomaterials chapter in Vision 2035 roadmap on materials of TIFAC, DST, India released in 2016, provides a clear roadmap to achieve such visions.[6] Current governmental initiatives such as "Make in India" campaign from 2015 provides the platform to achieve such visions.[7] First of all, for developing new "indigenous medical technologies", following things are important, (1) understanding the clinical scenario, (2) recent developments in technology landscape and (3) setting new goals as per indigenous clinical requirement. Secondary to that, for "decentralisation of emergency care", following things can be done using pharmacists, (1) Pharmacists with technological background such as (B Pharm and M Pharm) can be trained towards R&D and commercial production of the trauma care technologies, (2) Pharmacists with clinical background (Pharm D) can be trained towards the rational use of trauma care. Pharmacists are already part of public health (PH)[8], as well as in emergency care.[9] The Indian academic model[8], like any other international pharmacist training provides both the technological as well as clinical training.[9] In India, private and public

institutes are participating in this noble mission. It is a model for public resource pooling to achieve affordable healthcare.

DEVELOPING AFFORDABLE INDIGENOUS TECHNOLOGIES FOR CONTROLLING THE BLEEDING

Understanding the global clinical scenario of haemorrhage

As said earlier, the first step is to understand the clinical scenario. According to WHO, haemorrhage in traumatic injury cause, extensive bleeding, ischemia, permanent disability, stroke or even death; and is a major global problem.[4] This is the most common cause of death worldwide, leading to 5 million deaths annually.[10] Global statistics show that, 12% of mortality is due to violence or accidents. Haemorrhage is responsible for 30 to 40% of these deaths. Haemorrhage also leads to mortality in 33 to 56% in various cases during pre-hospital period.[11,12] It accounts for 80% of deaths in the operation theatre.[13] Uncontrolled haemorrhage in the first 48 hours just after the admission is responsible for all trauma related deaths.

Haemorrhage is a clinical situation; in which blood loss is high due to injury of major blood vessels.[14] To get a bigger perspective about the situations of haemorrhage the larger spectrum need to be seen. Classification of haemorrhage can provide the bigger spectrum. Based on risk, trauma injuries are classified into mainly 4 categories: (1) Severe-immediately life threatening e.g.: chest trauma, abdominal injury, (2) Emergent-injuries requiring surgical intervention within 6 hours to save the life, e.g.: open fractures, (3) Urgent- immediately life threatening; e.g., During surgical intervention within 24 hours and (4) open fractures-not life threatening immediately, with chances of permanent disability, e. g. closed fracture. In these cases, immediate hospitalization is the most sort-out measure. Based on source of injury, haemorrhage is classified into (1) Post-operative haemorrhage; occurs after the surgery, (2) Postpartum haemorrhage; after child birth; Both of this happens in a hospital setting are controllable, (3) Arterial haemorrhage; arises from the artery, (4) Venous haemorrhage; arises from the veins and (5) capillary haemorrhage; arises from the capillaries; the arterial and venous haemorrhage are fatal and needs immediate pre-hospital care. Depending upon the method of blood leak, haemorrhage is classified as, (1) primary haemorrhage; in the case of bleeding immediately after an injury, (2) reactionary haemorrhage; delayed bleeding after the injury, (3) secondary haemorrhage; delayed bleeding from sepsis, (4) Hematuria; blood in the urine from urinary bleeding, (5) Haemoptysis; coughing up blood from the lungs and (6) Hematemesis; bleeding in stomach. From the visibility of source of blood leak it can be classified into (1) internal haemorrhage; source not known and (2) external haemorrhage; source of blood leak is visible.[15-17] Internal haemorrhage generally occurs after collision due to the damage of the internal organs and internal large blood vessels. Wherein, the source of injury leading to blood loss cannot be seen, and it is very hard to recognize with symptoms.[15] These wounds are generally complex with hematomas. Thus, immediate hospitalization is the best sort out way for rescue.[17] On the other hand, external haemorrhage refers to blood coming from open wounds.[18] In both internal and external haemorrhage, snap stopping of bleeding is important to refrain from morbidity and mortality.[19, 20]

This review focuses on external haemorrhage, particularly bleeding from limbs. External bleeding from limb extremities occurs in traumatic injury after accidents.[3] It is fatal (life-threatening), and is very common after road accidents and in war.[21] The injury of major blood vessels and extensive bleeding are cardinal symptoms. Combination of FAs that can apply pressure on these blood vessels to reduce flow of blood such as tourniquets and FAs induce haemostasis such as elastic adhesive bandages and absorbent bandages are very effective in this case.[3-5, 22] The choice of FAs varies depending upon the nature of bleeding from external wounds and is constantly advancing (table below).[3]

Even though these aspects are well known, the availability and accessibility of such FAs is a major problem in rural side of both the India and other developing countries.[22] Thus, there is a need for adding such FAs into local healthcare units, personal FA kit or ambulatory care. Subsequently, new FAs for self-administration or FAs with minimum assistance to stop bleeding is most desired in a rural setting.[22] After understanding the clinical scenario, it is set to analyse the recent developments in technology landscape.

Recent developments in technology landscape of FAs for stopping bleeding

Stopping the bleeding from external injuries is the key to reduce the mortality and morbidity after haemorrhage.[24] This is conventionally being achieved using first-aid (FA) kits. Recently, the concept of FA kit is advancing. From FAs, the systems are being modified into point-of-care (POC) systems. The POCs are engineered systems aimed to manage multiple aspects. In this case, new POCs are designed not only to stop the bleeding but also to help in enhancing wound healing and tissue regeneration. The very common examples for POCs are the fire alarm, mask, patches, blood-glucose/urine strips and RBC counter. In all these cases, POCs are performing specialised functions to provide valuable information/intervention that help in improving health without much human motivation. These POCs are derived from earlier generation direct testing/intervention methods. From this discussions, it is apparent that in the future, technology landscape of FAs will be advancing from simple systems to more engineering based POC systems. Advanced FAs or POCs for haemorrhage are already available, that include military emergency tourniquets, blood-transfusion sets, advanced bandages like elastic adhesive bandages and absorbent bandages.[4]

PRINCIPAL ASPECTS OF CONTROLLING EXTERNAL HAEMORRHAGE [3, 23]

Factors	Arterial bleeding	Venous bleeding	Capillary bleeding
Characteristics of bleeding	Blood flow originates from artery. Blood red to yellowish in colour. Blood exist the wound in spurts, rather than steady flow.	Blood originates from vein. Blood blackish in colour (due to low oxygen content). Blood exists in a steady manner.	Happens in superficial wounds such as abrasions. Colour varies from red to blackish in colour. Generally oozes in small amounts as opposed to flowing or spurting.
Nature of risk	Life-threatening, Artery damage, Copious loss in short time, difficult to control.	Life-threatening, venous damage, Copious loss in short time, controllable through pressure points.	No life risks, Superficial.
Methods of control of bleeding	Direct pressure, elevation, indirect pressure, and the use of a tourniquet.	Direct pressure, elevation, indirect pressure, and the use of a tourniquet.	Direct pressure.
FAs used for controlling bleeding (choice)	Pressure bandages< Tourniquets.	Pressure bandages < absorption bandages < Tourniquets.	Pressure bandages < absorption bandages.

New research in this area is happening to reduce human motivation and value-addition by appropriate engineering of these systems. Pharmacological agents containing spray systems are an example.[25] Subsequently, the new POCs are aimed to self-administer for stopping bleeding until reaching to the hospital. All scenarios of haemorrhage cannot be met with one solution, subsequently multiple solutions are required.

The field bandage is an advanced FA or POC system used to control the external bleeding by military people; it is made of adsorbent cotton which is stuffed inside several layers of gauze. It absorbs a large volume of blood and causes platelet aggregation; thus achieves blood coagulation.[26] On the other hand, elastic bandages absorb up to 50 cc of blood, it is used to control bleeding even in head injuries.[27] The elastic and adhesive bandage is another advanced FA or POC used to control the bleeding by interacting with blood components; particularly with platelets inducing aggregation while exerting constant pressure to slow down the blood flow.[27] A recent review says that, the bandages for stopping bleeding is joining hands with wound healing bandages. This is an example for developing new technologies by combining systems.[28] The applications of pressure using hand or finger to the site against the bones which are proximal to bleeding site are an intervention to stop bleeding, traditionally used. The early usage of some drugs has proven that they have an immediate effect on clotting of blood at open wounds and thus stops bleeding.[29] Typically, the bleeding from an arm or leg is usually be controlled by emergency trauma dressing, manual direct pressure, elevation or using tourniquet.[30] In some situation, a tourniquet is applied first, since other methods will not be adequate to control the bleeding. Analysing the technological sophistication of new FAs, it becomes apparent that, the clinical observations in trauma care together with the recent research efforts have resulted in a new appreciation for the role of inducing clotting using advanced biomaterials for assisted haemostasis,[31] in addition to pressure assistance. For rural world, in addition to the technological sophistication the accessibility and affordability of these advanced FAs or POCs need to be improved.

TECHNOLOGICAL REQUIREMENTS OF POC FOR TRAUMA CARE FOR NEW AFFORDABLE AND ACCESSIBLE SYSTEMS

Advanced First-aids or POC systems that are self-administrable are the most appropriate choice for stopping blood from external haemorrhage of limbs.[32] These POC systems are usually biomedical technologies based on advanced biomaterials that act by (1) reducing the blood flow rate[5] as well as (2) inducing clotting by assisted haemostasis.[31] The right property of the ideal POC system for haemostasis of external bleeding of limb injury varies depending upon the situation. The various situations that need independent attention are, (1) region and type of injury, (2) specific patient population, (3) procedure, (4) type of bleeding and (5) specific mechanism of action of agents.[33] The POC should essentially, (1) rapidly and effectively control bleeding, (2) effectively contact the bleeding surface and induce coagulation, (3) work well and in a reliable manner, (4) easy to handle, (5) simple preparation techniques, (6) available in multiple delivery options, (7) compatible with patients physiology, (8) ensure safety,[33] (9) cost effectiveness and (10) produce minimum damage to the neighbouring tissue. In future, it can extend the borders to improve wound healing and tissue regeneration.[28] From a bigger perspective, the advanced FAs or POC for haemostasis should also be aimed to (1) enhance the treatment, (2) provides improved long term outcome and (3) ensure reduced stay in hospitals. These aspects need to be properly addressed in comparison to the commercially available controls in terms of effectiveness, safety and cost.

Recent surge in research and development of advanced FAs and POCs brings out new technologies. However, the sophistication along with patient variabilities makes the haemorrhage care case-sensitive. In this scenario,

appropriate decision making and rational use of POCs or drugs become increasingly important. [34] Generally, such FAs or POCs are distributed to first hand users. The first hand users or provider network are ambulatory care, trauma centres, trauma patient care, pharmacies and clinical forensics to general public.[35] Provider network reinforces that, advanced FAs and POCs could save life and organs after injury and bleeding.[36] Pharmacies and pharmacists can play an important role in the rational use of these haemostatic technologies and extend their services in public health (PH).

PHARMACISTS EMERGING ROLE IN RURAL EMERGENCY CARE AS R&D PERSONAL AND SERVICE PROVIDERS IN HAEMORRHAGE CONTROL

Trauma care in rural India and pharmacists emerging role

In developed countries, trauma care management team is a team of clinicians with accompanying support.[37] On the other hand, in developing countries, such facilities are available only to urban side. In rural country side, health care is mainly depends on traditional medicine; where emergency care is a nightmare. They always face inadequate healthcare due to low income and lack of knowledge[38-40] clinics as well as transportation facilities.[38, 41, 42] In developing world, overall number of physicians, health workers and hospital beds are almost 1/10th of that in developed countries.[41, 42] In these rural areas, after accident, as the time elapses from 20min to 120min the probability of death increases from 5% to 27%.[42] Fortunately, after doctors the pharmacists are the most common healthcare personal in rural India.[42]

Orienting pharmacists for the bigger mission in healthcare

In the past, "compounder", used to play an important role in Indian rural healthcare as community pharmacists.[43] The compounder is evolved to today's pharmacist. Pharmacists provides optimal pharmacotherapy, manages chronic patients, participate in emergency care in rural areas, in Indian scenario. They are often act as the centre pillar of patient centred (personalized) medicine aspects of modern medicine.[44, 45] Utilising their services is particularly important in remote rural areas, with lower number of clinics, but having pharmacies. Developed countries such as Canada, US, and UK have long been exploring pharmacist services in rural health care. For example, recently, UK starts focusing on exploring pharmacist services for emergency care. The Royal Pharmaceutical Society in their recommendations emphasized the importance of including pharmacists in accident related emergency care.[45] The pharmacists are systematically trained to understand, (1) the biological as well as therapeutic aspects of chemical molecules like drugs, (2) its design, development, and formulation, and (3) its administration and various physiological and as well as toxicological effects.[46] Today, in rural side, pharmacists are the next sort healthcare personal after doctors, who can significantly contribute towards affordable therapeutics and practice of over the counter medicines. This is because of their comprehensive training in technological aspects of pharmaceutical agents and its rational use in clinics. Recently, WHO introduced the concept of "seven star pharmacist", which identifies pharmacist as a care-giver, decision-maker, communicator, teacher, researcher, leader, life-long learner and manager. This is later taken up by FIP in 2000 in their policy statement.[47-49] The future pharmacists need to be essentially the said "seven star pharmacist", for shaping up the pharmacy profession for future to maintain the dignity of modern medicine, by advocating and practicing "rational use of medicine and therapeutics".

Pharmacists as public health practitioners for campaign based programmes

Activities focusing on betterment of people's health are public health (PH), and pharmacists are an integral part of it. The voluntary PH life for orienting towards "seven star pharmacists" starts at their undergraduate level as per any international curriculum[50, 51] and in many renowned pharmacy schools in India such as Amrita School of Pharmacy; Amrita University[52] and Annamalai University.[53] International Pharmaceutical Student's Federation (IPSF) is actively participating in PH over 50yrs; supported WHO Stop TB Partnership, participates in different campaigns related to HIV-AIDS, Tobacco alertness, TB awareness and world health day over 50yrs.[54] Recently, antibiotic stewardship is being taken up by the pharmacists.[54] In the past, Indian Pharmaceutical Association (IPA) and Commonwealth Pharmaceutical Association have joined hands with IPSF to counsel rural Mumbai about strict medication for TB through the "TB fact card project" between 2005-2006.[55] Pharmacists with clinical pharmacy training (e.g. Pharm D, M Pharm (Pharmacy practice), Pharm D PB, B Pharm with clinical pharmacy and hospital pharmacy training, are professionals sufficiently trained in safety and efficacy aspects of pharmaceuticals as well as rational use of medicine.[43] This along with a tailor made training in campaign programme in respective therapeutics make pharmacists the practitioners of personalized medicine.[43, 54] This campaign based tailoring of healthcare professionals is widely practiced in India, and is highly successful.[54, 55]

Emerging trend in curriculum of pharmacist and its robustness

The introduction of Pharm D program by PCI had given impetus to clinical and hospital pharmacy practice in India.[56] This is one of the major achievements for pharmacists in recent years. Within the very short span (<10yrs) the newly trained clinical pharmacists are joining doctors for improving medication practices.[47] Now leading hospitals are hiring clinical pharmacists to keep a watch on treatment associated mortality and morbidity rates. Patients are happier with the personal care of

pharmacists. The era of dormant clinical pharmacy profession in India is over; the future is towards "seven star pharmacists", who has gained independence to advocate and practice "rational use of medicine". The current trend in India is, In addition to Pharm D, several clinically trained B Pharm, M Pharm graduates depending upon their degree of clinical exposure is also getting accommodated to secondary or tertiary care.[8] In the near future, Pharm D will be playing the lead role of clinical pharmacy in hospitals. At the same time, community pharmacies will still be the same for some more time. The pharmacy practice training provides clinical experience to the pharmacy students and provide academic and research background for the rational use of therapeutics. During the training, they are getting exposed to medication aspects; ranging from home medication to critical care. They are being trained to be vigilant about patient response to treatment, ensuring affordable healthcare plausible.

Indian Pharmaceutical education now has two facets, (1) Pharmaceutical technology training and (2) Clinical pharmacy practice training.[43] The specialization in pharmacy education starts after a thorough teaching about various aspects of pharmaceutical profession at undergraduate level (initial 4yrs).[43] The training in pharmaceutical technology provides the chemical, physical and biological aspects of designing, developing, formulating and practicing medicines. It also teaches the role of pharmacist in various aspects of drug supply chain and the rational use of drugs. The general principle of understanding attained through the curriculum is that, the drugs need to be said in terms of "percentage impurity" not based on "purity of substance" and is a highly regulated field that requires rational use of medicines for safety reasons.

Training pharmacists in R&D and emergency care using POCS

Indian pharmaceutical education model provides enough flexibility for the students to choose industry, clinics, academics or research like any international curriculum.[4] Their knowledge can easily be extended to emerging healthcare disciplines. Biomaterials are identified as a strategic sector that can contribute in the GDP of the country as per Vision 2035 roadmap on materials by TIFAC, DST, India.[41] This is based on the research and development happening in biomaterials for developing various clinical solutions. Biomaterials with engineering principles for developing new structures[57-60] is now being explored for extending the border of therapeutics [61-65] and diagnostics[66] extensively. Also, biomaterials play an important role in technologies using for stopping bleeding.[67,68] The chemistry, physics and biology of biomaterials are similar to molecules such as drugs and proteins, when comes to therapeutics. This knowledge about biomaterials, the pharmaceutical students can very easily learn and comprehend.

Through appropriate short course-work, pharmacists can be introduced into biomaterials field. Academic training that follows to project training in peer-institutes can provide the required skill set for exploring the biomaterials in industry or clinics. Most importantly, training programmes for PH in rural country side will be most impactful from a service perspective.[26] The essence of training should be to, (1) understand the details of case sensitiveness of bleeding and what technologies will be more appropriate, (2) The process involved in the R&D of these materials and technologies and (3) How to extend the impact of golden hour using latest technologies. With this training, pharmacists can be interfaced with clinicians, engineers, and chemists to develop advanced POCs and for their rational use in rural side.

Current proactive policies by government for improving healthcare

The "Make in India" campaign is highly successful in encouraging new technologies from India.[69, 70] It helps the foreign direct investment of the country.[71] Biomedical industry is a knowledge driven industry that needs resource support and in that manpower with adequate skills is an important factor. Understanding these factors and exploring these opportunities are providing limitless scope for pharmacists both from social and professional perspective.

CONCLUSION

In conclusion, "Make in India" campaign is an opportunity for pharmacists to show their leadership skills in terms of R&D and rational use of advanced PAs or POCs for public health. Pharmacists are practicing campaign programmes globally in the past. This is another call for pharmacists to help the rural world to address their emergency care, particularly haemorrhage after traumatic injury. Indian pharmaceutical education provides robust training for R&D as well as clinical practice of therapeutics. That training can easily extended to biomaterial science and technologies for trauma care. The TIFAC-2035 vision document foresees biomaterials as a strategic sector that can contribute towards GDP. New and advanced biomaterials need to be prepared with respect to clinical requirements for that purpose. Understanding clinical requirements is required for developing new clinical solutions. Care of haemorrhage in traumatic injury needs more attention in rural country side of developing world and new technologies are required for that. Along with that, there exists a requirement of rational use of such technologies for improving accessibility. Pharmacists can easily be trained to develop such technologies for affordable health care. For acute interventions to stop bleeding, advanced bandages and pressure assisted techniques are needed. These systems need to be improved addressing its current limitations and made affordable for accessing to larger population. Understanding the said opportunity, first of all, pharmacists need to be trained in technology development of advanced FAs or POCs to stop bleeding,

later towards rational clinical practice of such POCs in rural scenario.

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