INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

May 2019

Comic Corner

YOU JUMP, I JUMP – HMM... MAYBE NOT

Lifestyle and Sports

SORE TODAY, STRONG TOMORROW

Good Science Can Produce Unexpected Results:

PERSPECTIVE FROM FELLOWSHIP

TRIPOD and INA-PROACTIVE Studies' Updates

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2019

INA-RESPOND Steering Committee Meeting

@Novotel, Tangerang — 10 April 2019

INA-RESPOND newsletter

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content

May 2019 Edition | issue #68

FEATURES

INA-RESPOND Newsletter

TRIPOD & INA-PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Maria Intan Josi, M. Ikhsan Jufri, Venty Muliana Sari

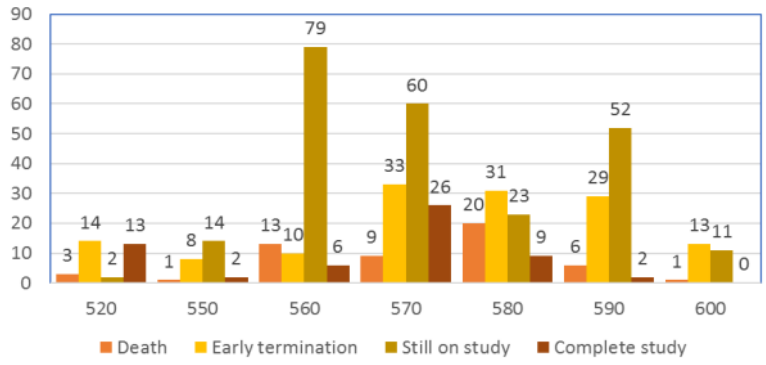


Figure 1.Participant status per site based on uploaded CRF per 31 Mar 2019

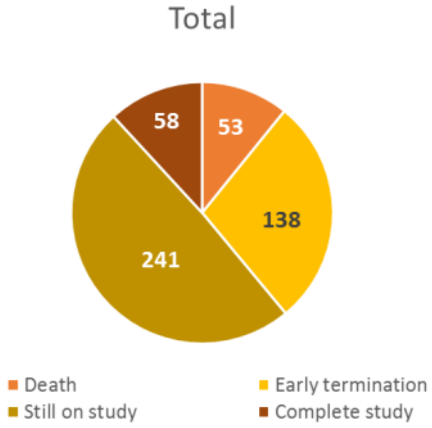


Figure 2. Total Participants Status based on uploaded CRF per 31 March 2019

STUDY UPDATES

INA102

PARTICIPANT STATUS

Per 31 March 2019, the total ongoing participants in TRIPOD study are 241 out of 490 enrolled participants. Fifty eight participants have completed the study while 191 participants were terminated early (including death). Therefore, there are still 49.2% participants from the total enrolled participants in the follow-up status. From the uploaded CRFs, there are two participants from site 520 (RS Sanglah, Denpasar) who still need to be followed up; 14 participants from site 550 (RSUP dr. Wahidin Sudirohusodo, Makassar); 77 participants from site 560 (RSUP dr. Kariadi, Semarang); 60 participants from site 570 (RSUD dr. Soetomo, Surabaya); 23 participants from site 580 (RSUP dr. Sardjito, Yogjakarta), 52 participants from site 590 (RSUP Persahabatan, Jakarta); and 11 participants from site 600 (RSUP dr. Adam Malik, Medan).

Site	Waiting for Baseline Study Culture Result	Waiting for Baseline DST Result
520 (n=32)	Complete	Complete
550 (n=25)	Complete	Complete
560 (n=108)	Complete	3 (estimation: May 2019)
570 (n=128)	11 (estimation: Feb 2019)	11 (estimation: May 2019)
580 (n=83)	6 (estimation: Feb 2019)	7 (estimation: May 2019)
590 (n=89)	1 (estimation: Feb 2019)	1 (estimation: May 2019)
600 (n=25)	Complete	Complete

Figure 3.Culture and DST results up to 30 April 2019

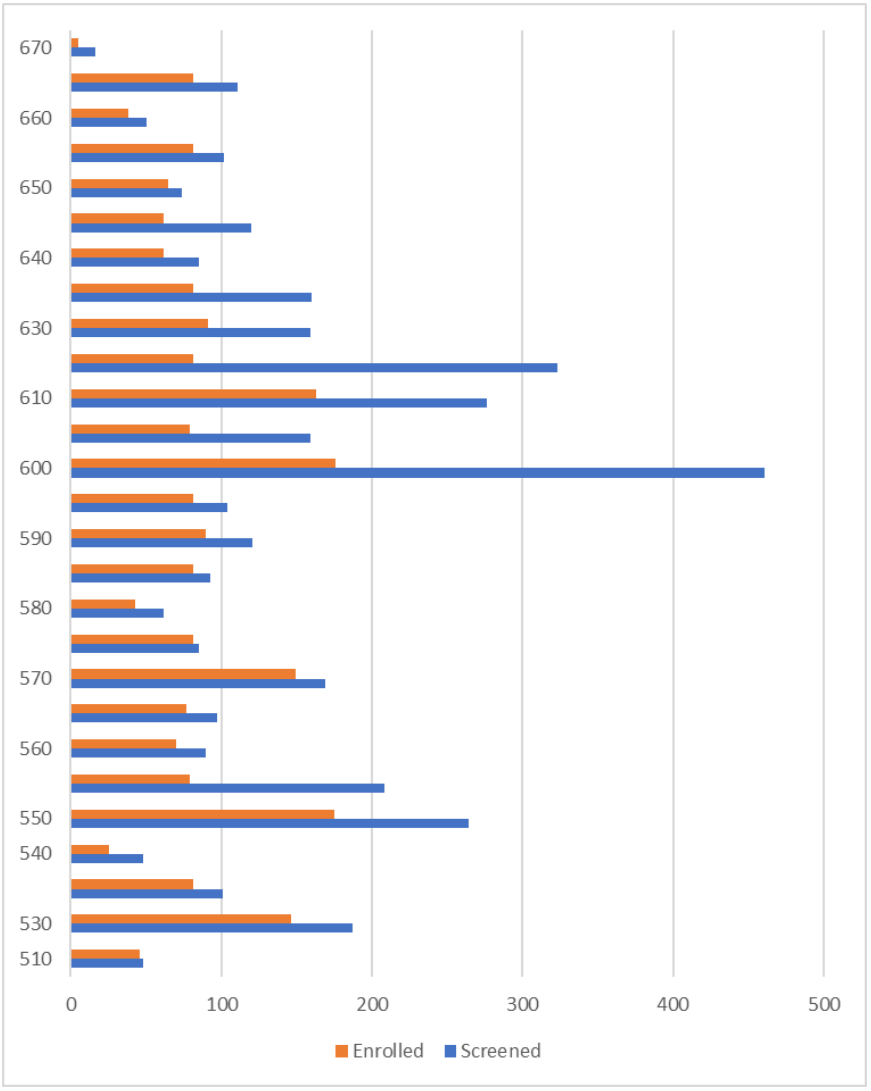
INA104

On 5 Apr 2019, RSUD Zainoel Abidin, Aceh (RSUDZA) became the 15th site of our INA-PROACTIVE study and enrolled its first subject on 9 Apr 2019.

The total number of subjects enrolled up to 28 Apr 2019 is 2,289, consisting of 2,189 adults and 100 pediatrics. The enrollment rate is 60.66% from entire screening (3.773 patients). Details are shown in Figure 1. The enrollment failure rate was 39.33% from total screening. Information on the reason for failure is shown in Figure 2.

We have done two 2nd monitoring visits in April, to Site 580 RSUP Dr. Sardjito, Yogyakarta on 22-24 Apr 2019 and Site 640 RS St. Carolus, Jakarta on 24-26 Apr 2019.

For site preparation update, site 680 – RSUD dr Soedarso, Pontianak is still waiting for the schedule of Site Initiation Visit (SIV). The SIV is planned to be conducted by the end of May 2019. We have also planned to do Site Preparation Visit to RSUD Abepura, Papua on 13-15 May 2019 and to RSUD TC Hillers, Nusa Tenggara Timur on 22-24 May 2019. Hopefully, INA-PROACTIVE will soon have new active sites representing the eastern part of Indonesia.



Reason for Failure	510	530	540	550	560	570	580	590	600	610	630	640	650	660	670	Total
Suspect HIV	0	0	0	4	0	0	0	0	1	5	5	0	0	4	1	20
Refuse to consent or not cooperative	0	3	2	4	7	0	9	7	1	2	0	10	2	2	0	49
Unwilling to comply with study procedure	0	25	1	2	17	4	2	0	28	23	0	9	5	2	0	118
Plans to move away	0	6	1	10	7	0	0	4	12	4	10	15	1	3	1	74
A. No Show	1	21	14	72	2	2	4	19	303	203	65	43	0	7	7	763
B. Busy/ in a hurry	1	4	5	32	3	6	0	4	7	20	5	4	14	18	2	125
C. Has been enrolled	0	0	0	85	4	9	8	18	13	84	56	0	8	6	0	291
D. Participated in other study	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
E. Hospitalized or unwell	0	0	0	8	0	0	8	2	0	0	0	0	0	0	0	18
F. Other: Specify (e.g. no referral letter from other health facility, equipment trouble)	0	2	0	1	0	3	0	0	0	14	6	0	0	0	0	26
Grand Total	2	61	23	218	40	24	31	54	365	355	147	81	30	42	11	1484

Figure 2. Reason for Failures

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POLICY BRIEF WRITING WORKSHOP

By: Nurhayati

In general, this workshop trains participants to compile policy brief as a short document that presents findings and recommendations from research to be addressed to policymakers, and also serve as a tool in conveying input to policy. The Policy Brief writing workshop was held by the Tempo Institute at Harris Sentul Hotel, Bogor on 28 - 30 April 2019. Tempo institute is part of Tempo Group Inti Media that focuses on developing journalism and communication. Its activities are to organize various writing training, ranging from writing opinion classes, designing infographics, intensive journalistic courses, etc. One representative from INA-RESPOND, sponsored by USAID, has been allowed to take part in this series of workshops.

Policy brief writing workshop @Harris Sentul Hotel, Bogor

One of the researchers' primary objectives is for the results of the research to be useful and become evidence to be used by policymakers in making policy. For the results of his research to reach the policy maker, a comprehensive dialogue needs to be made so that the policy recommendations target the right targets and objectives are achieved. Therefore, the policy brief was prepared to provide considerations for various policy options to officials/ leaders of government politicians, donors, etc. This policy brief is targeted at readers who have limited time in making decisions and are made to facilitate the stakeholders to understand and respond to the recommendations submitted.

The presentation was opened by Dr. Muhammad Taufiq (Deputy for Competency Dev Policy), talking about the basics of making an interesting policy brief. Dr. Untung Suseno (the Center of Analysis of the Determinants, Ministry of Health) continued the presentation by sharing his experiences on how to develop evidence-based policy briefs and providing some useful tips in submitting policy briefs at the Ministry of Health. Following topics were given from the Tempo Institute team about the principles of writing policy briefs and their anatomy techniques, mind mapping techniques (ideas and angles), data research techniques, and processing and transforming data into infographics.

In principle, the policy brief must be made interesting, relevant, practical, and easy to understand. The right time in submitting a policy brief is also crucial seeing that the time to draft a budget for each institution is different. So that readers do not need to have specialized knowledge or additional reading to be able to understand it, the policy brief should focus on a topic with only one question, made as many as two to four pages in deductive structure and attractive design. The title is written in an active sentence. It should be dynamic, compelling, and directly describe the problem. The executive paragraph is in the first paragraph to show the importance of policy brief. It is made with the concept of who, what, where, when, why, and how. The sentence made must be effective following the rules of correct spelling (ejaan yang disempurnakan). Avoid displaying numbers and jargons in the initial paragraph. To be more productive, use relevant visuals using infographics so that images can speak for themselves well. Sort out the research data and the results of the analysis that support the facts to support the recommendations.

I learned a lot from the 3-day workshop. The topics presented in this workshop are exciting, and they are presented interactively, so the learning process goes two ways.

The learning process does not stop here. Armed with lessons learned, each participant will be accompanied by a mentor from Tempo institute to complete the policy brief according to the topics brought from each institution. The mentoring and discussion process will continue for ten days to get one policy brief.

Overall, this workshop was beneficial, and there were a lot of new things that can be put into the making of a policy brief. Thank you to USAID for sponsoring me to be able to take part in this workshop and also appreciate the Tempo institute for giving knowledge and sharing their experiences in this workshop.

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SITE PROFILE: RSUP DR. KARIADI, SEMARANG

By: M. Rosyid Ridho

Semarang is the capital of Central Java Province and a touristry city full of various exciting stories and cultures. One of the INA-RESPOND network research sites, FK UNDIP/RSUP Dr. Kariadi's, is located in this city. The site is led by Prof. dr. Muhammad Hussein Gasem, Sp.PD K-PTI, who is also a Steering Committee member of INA-RESPOND.

Prof. dr. Muhammad Hussein Gasem, Sp.PD K-PTI is an expert on infectious and tropical diseases who has written many research works. Many of his writings related to leptospira disease, Clostridium difficile, typhoid fever, community-acquired pneumonia (CAP), etc. have been published in national and international journals. He is a member of the INA-RESPOND Network Steering Committee and the INA-RESPOND Principal Investigator for AFIRE Study. He has high expectations that through the presence of INA-RESPOND, medical staff and teaching staff in the medical faculty of Universitas Diponegoro (FK UNDIP) and RSUP dr. Kariadi will be more interested in conducting research.

Site 560 joined INA-RESPOND network in 2011 and has actively participated in several studies since. The past studies were AFIRE (The Etiology of Acute Illness Requirement Hospitalization); TRIPOD (Tuberculosis Research of INA-RESPOND on Drug Resistance); Pneumonia in Pediatric - a PEER Health study [Implementing a Combination of Clinical Rapid Parameters (Diagnostic, Biomarkers and Standard Care Procedures) for the Etiology Diagnosis of Pneumonia in Pediatric Patient to Improve Clinical Management in Indonesia]. Currently, our site is actively participating in PROACTIVE ("A Prospective Observational Cohort Study on HIV Infection and Risk Related Coinfections / Comorbidities in Indonesia). This proves that site 560 has the enthusiasm and is ready to collaborate with other centers in developing science, especially in the world of health research.

The PROACTIVE study, which is expected to be the masterpiece of the INA-RESPOND research network, requires support and collaboration from all parties. The high number of patients in Central Java can be seen from the number of patient visits at RSUP dr. Kariadi (above 680 patients per year with several new patients above 30 patients.)

Prof. dr. Muhammad Hussein Gasem, Sp.PD K-PTI

Dr. Nur Farhanah, Msi, Med, Sp.PD K-PTI leads the PROACTIVE team at RSUP Dr. Kariadi with Co-Principal investigator Dr. Muji Rahayu, Msi.Med, Sp.PK; dr. Nahwa Arkhaesi, Msi.Med, Sp.A, DR .; and dr. Muchlis Achsan Udji Sofro, Sp.PD, K-PTI. This research was supported by 3 Research Assistants (Dr. M. Rosyid Ridho, Dr. Niken Maretasari Putri Atmojo, and Dr. M. Tri Sutrisno), 2 Lab Technicians (Tri wahyunintyas, Amd.Ak and Bayu Supramantoro), and 1 Study Nurse (Ngatno, Amk)

Dr. Nur Farhanah, MSi.Med Sp.PD K-PTI cares about the course of a study. She often intervened in solving problems at the site. She has a loving nature and cares for everyone involved in the research. She is also firm and wise. Aside from being a doctor at RSUP dr. Kariadi, she is also a very friendly lecturer. Dr. Nur Farhanah is currently researching the main topic of SEPSIS as her doctorate thesis. She is also actively involved in teams and working groups in the hospital or university environment.

Dr. Muji Rahayu, M.Sc Med, Sp.PK is a clinical pathologist who is reliable and full of totality. She is also friendly and patient. She loves new things and is always eager to accept new challenges. Her enthusiasm to learn the latest knowledge is unquenchable. Now, she is pursuing studies related to stem cells.

Dr. Nahwa Arkhaesi, M.si.Med, Sp.A is a doctor who is very patient, friendly, and caring about others. She can be friends with all circles. Co-As doctors always pray to get her as an examiner. When talking to her, she often talks about the values of life.

DR. dr. Muchlis Achsan Udji Sofro, Sp.PD K-PTI is a doctor who is humble, friendly, and compassionate to all people. He is very active and involved in several local and national work teams. He often gets swamped and had to move around the city to attend many meetings in one week. He is currently the Chair of the RSUP HIV Team, Dr. Kariadi, Coordinator of the KPA CST Working Group in Central Java Province, Member of the Indonesian Ministry of Health's HIV expert panel, member of the antibiotic resistance control program

Dr. Mohammad Rosyid Ridho is one of the Research Assistants (RA) who is currently on duty at site 560. The involvement of dr. M. Ridho started in 2014 when he replaced Dr. Venty and Dr. Annisa at AFIRE research. He temporarily left INA-RESPOND to work in several NGOs and re-joined in 2017 in pediatric pneumonia research (PEER Health), and later, in the PROACTIVE study. While working as an RA, he had many memorable stories.

Dr. Niken Maretasari Putri Atmojo, who was born in Purworejo, is the second child of two siblings. She is a friendly and passionate young doctor who dreams of becoming a Pediatrician. She was very excited to take part in poster competitions at scientific events. By joining INA-RESPOND, she hopes to add his experiences in the international research field.

Dr. M. Tri Sutrisno is an agile and diligent young doctor who is expected to be the RA successor at site 560. As an RA, he is expected to be more alert and responsive to future problems. He is religious and is good at making posters or decorative art. Hopefully, with his passionate young spirit, he can influence other researchers to work and carry out their responsibilities properly.

The PROACTIVE study at site 560 has two dedicated and diligent Technician Labs. They are **Ms. Trie Wahyuningtyas** and **Mr. Bayu S.**; both are full-time analysts at RSUP Dr. Kariadi. Hopefully, this study can have benefits for patients and the Indonesian Ministry of Health, especially in the efforts to treat and prevent infectious diseases in Indonesia.

Site 560 is only a small part of health research networks in Indonesia. Of course, we need to work together to improve the health of the people of Indonesia with the ultimate goal of improving welfare for all levels of the Indonesian people. It takes hard work, intelligence, and sincerity to realize all these things. Thank you very much for allowing us to join INA-RESPOND.

From top to bottom:

dr. Nur Farhanah, M.Si.Med, Sp-PD, K-PTI; dr. Muji Rahayu, M.Si.Med , Sp.PK;
dr. Nahwa Arkhaesi, M.Si.Med , Sp.A; DR. dr. Muchlis Achsan Udji Sofro,

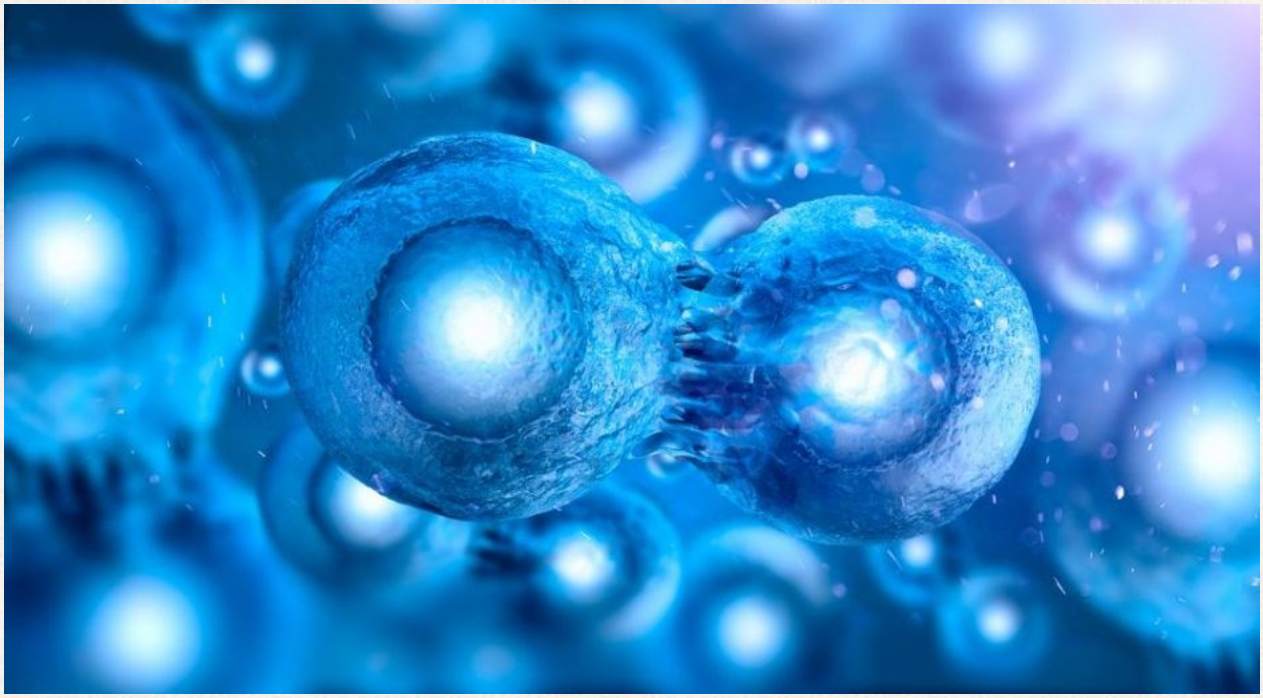
Site 560 gathering event: A farewell party for Dr. Erna Wang for her 2.5-year contributions in INA-RESPOND network

From upper left corner (clockwise): dr. M. Rosyid Ridho, dr. Niken Maretasari Putri Atmojo, dr. M. Tri Sutrisno, Ms. Trie Wahyuningtyas, Mr. Bayu S.

INA-RESPOND Newsletter

STEM CELL THERAPY FOR LEUKEMIA

By: Muji Rahayu



FROM OUR LABORATORY

The human body consists of cells and always works all the time. This causes cell damage which can cause its function to be disrupted. Also, one day the cells will also age which eventually lead to degenerative diseases. Cell therapy that is currently developing in Indonesia will provide great hope for these disorders. Some types of cell therapy include stem cells, blood cells (erythrocytes, platelets, and leukocytes), cell immunotherapy (B cells, T cells, NK cells, cytokines, etc.).

Stem cells are new cell sources. They can differentiate into new cell types. The stem cell will divide to multiply or become another cell. Types of stem cells based on maturation are divided into two, namely embryonic stem cell and adult stem cells. Embryonic stem cells are the beginning of all types of cells in the body. Adult stem cells are stem cells that are found among other cells that have differentiated, in a network that has undergone maturation. Adult stem cells can be found in hematopoietic stem cells, cardiac stem cells, neural tissue stem cells, skin cell mesenchymal stem cells, etc. Stem cell therapy is now being carried out. Some hospitals have carried out stem cell therapy that was previously conducted by Research first. Some therapies that use stem cells, for example, for the treatment of hematological malignancies, treatment of burns, for the treatment of diabetes mellitus, osteoarthritis, etc.

Stem cell therapies in hematological malignancies, which are called bone marrow transplant therapy (bone marrow grafts), have been carried out in several hospitals (RSCM, Darmais Hospital, Sutomo Hospital, RSUP Kariadi, etc.). Hematopoietic stem cells that will be used for treatment in hematological malignancies will first be prepared, including stem cell mobilization, isolation, harvesting, processing, ablation, thawing, stem cell infusion. The preparations are done to get good stem cell products (sufficient amount, its viability is met, and stem cells can grow).

STEM CELL

A stem cell is a cell that has not differentiated and has a very high potential to develop into many different cell types. Stem cells are used to replace cells in our body that are damaged for survival. Stem cells will develop in accordance with damage to existing cells such as blood cells, muscle cells, bone cells, skin cells, etc. Some diseases that can be cured with stem cells include leukemia, OA, bone

	Embryonic stem cells	Adult stem cells
Source	Inner cell mass	Somatic cell population
Potential differentiation	Pluripotent	Multipotent
Proliferation potential	++	+
Insulation	Easier (all cells belonging to the mass in the cell are embryonic stem cells)	More difficult (concentration / comparison with adult cells in the network is very small)
In vitro culture	easier (supported by higher proliferation abilities and more standardized procedures)	More difficult (due to lower proliferation capabilities and procedures that are still being optimized)

abnormalities (spinal cord injury). Some others are still in research: cancer, heart disease, Parkinson's disease, multiple sclerosis, stroke, Huntington's disease, etc. Stem cell treatment must be done carefully, and of course, at large hospitals that have conducted stem cell research and get good results. At present, several stem cell transplants have been tested by scientists and proved to be safe and effective. For examples, bone marrow transplants, stem cell therapy in bone surgery and plastic surgery section whose Clinical Practice Guide has been submitted by the collegial to the ministry of health.

Types of stem cells based on the maturation level are divided into two: embryonic stem cell and adult stem cells. Embryonic stem cells are the beginning of all types of cells in the body. Adult stem cells are stem cells that are found among other cells that have differentiated, in a network that has undergone maturation. The difference between embryonic stem cells and adult stem cells can be seen in the table above.

The source of embryonic stem cells is stem cells found in humans or animals that are still in a series of embryogenesis processes. Embryonic stem cells are inner cell mass contained in the blastocyst cavity.

At present almost all mature tissues and organs are proven to contain adult stem cells. Therefore, the classification of adult stem cells is based on an organ or cell group that will become the differentiation pathway. Adult stem cells can be found in hematopoietic stem cells, cardiac stem cells, neural tissue stem cells, skin cell mesenchymal stem cells, etc.

Hematopoietic stem cells are used for the treatment of hematological malignancies. Stem cell therapy in hematological malignancies has often been carried out in several hospitals (RSCM, Darmais Hospital, Sutomo Hospital, RSUP Kariadi, etc.), which are now known as bone marrow transplant therapy (bone marrow transplant).

HEMATOPOIETIC STEM CELL

A hematopoietic stem cell is a cell that can form all blood cell progenitors to process hematopoiesis and body immune functions. So that it can be said as a parent of all types of blood cells circulating in the human body. Hematopoietic stem cell isolation can originate from peripheral blood cells, blood and bone marrow. To determine the existence of hematopoietic stem cells by recognizing the expression of surface protein molecules (cluster of differentiation, CD). Based on the results of research, surface markers most often used as characteristics of hematopoietic stem cells are CD14, CD34 and CD45.

Stem cell group	Differentiation
Hematopoietic stem cells	Able to differentiate into all types of blood cells such as red blood cells, platelets, monocytes, neutrophils, basophils, eosinophils, etc.
Nerve tissue stem cells	Able to differentiate into three main groups of nerve cells, namely astrocytes, oligodendrocytes and neurons
Skin tissue stem cells	Able to differentiate into keratinocytes and constituent cells in the skin's epidermis
Mesenchymal stem cells	Able to differentiate into osteocytes, chondrosists, adipocytes and various types of connective tissue infusion cells
Heart stem cells	Able to differentiate into endothelial, cardiomyocytes, smooth muscle cells

Bone Marrow Transplant (Bone Marrow Graft).

Current hematologic malignancy has become a real problem in health care, with increasing cases of hematological malignancies being treated in wards and people seeking bone treatment transplants (bone marrow graft).

Bone marrow transplantation is a procedure where the damaged bone marrow is replaced with a healthy one. Damaged bone marrow can be caused by high-dose chemotherapy or radiation therapy. Bone marrow transplantation is also useful for replacing blood cells damaged

by cancer. Cancer bone marrow transplantation is based on an indication of the type of hematological abnormality and fulfills the conditions specified by the physician in hematology-oncology. Bone marrow transplant therapy uses hematopoietic stem cells that can be taken from Phifer blood stem cells (PBSC) or bone marrow). These hematopoietic stem cells can be inserted/infused stem cells into the patient's body, and there will be several actions: stem cell mobilization, isolation, harvesting, processing, thawing, stem cell infusion.

1. Mobilization

The clinician took action by providing stimulation of the hematopoietic growth factor (G-CSF, GM-CSF), so that blood stem cells will produce more blood cells in the bone marrow. These cells will also be removed in the peripheral bloodstream.

2. Stem cell preparation

Stem cell preparation is an action in the context of carrying out bone marrow transplantation starting from harvesting, handling before storage, and thawing process. The indication of stem cell preparation is

a. Get good stem cell products at -80 storage

b. Meet harvest requirements by:

a. PBSC (apheresis),

• CD 34 target 20-40 cell / microliter

• Harvest CD 34 target: 2x10 6 / kg body weight

b. Bone Marrow

• TNC target 2 x 10 8 kg / kg

2.1. Harvesting

Collecting or harvesting stem cells that have been mobilized, blood taken through PBSC (Pheriff Blood Stem Cell) by apheresis or harvesting can be done by taking blood from bone marrow by BMP. All CD 34 counts as a marker of stem cells. For the transplant to succeed, stem cells must meet the minimum and optimal requirements that can be obtained from one or several times.

2.2.Processing (hematopoietic Stem cell preparation)

Where do stem cell concentrations aim to facilitate further processing and cryopreservation? In order not to disintegrate at temperatures below 0 degrees, into the concentrate put in dimethyl sulfoxide (DMSO) 10% and autologous plasma for growth.

2.3. Assessment of the quality and viability of stem cells obtained

Besides having to fulfill the quality, the blood stem cells taken must also have optimal viability. The quality of stem cells is assessed by counting CD 34+ cells utilizing flow cytometry. This technique is fast and accurate, while knowing viability is assessed by 7AAD flowcytometry or by using trypan blue coloring.

2.4. Cryopreservation and stem cell storage

After undergoing secondary processing, blood stem cells must be stored at -80 degrees or -197 degrees in nitrogen to stay alive for long periods of months. In addition to storing in cryo bag, there are also stored in small tubes to assess quality periodically during storage.

2.5. Thawing

If the stem cell wants to be used after being stored in - 80 degrees or -197, then the blood must be thawed first by entering the water bath at 37 degrees.

Conclusion

1. Stem Cells are cells that have not differentiated and can develop into various specific cells

2. Based on the origin of stem cells, there are embryonal stem cells and adult stem cells

3. Adult stem cells can be found in hematopoietic stem cells, neural networks, mesenchymal tissue, skin tissue, and the heart.

4. Stem cells can be used to treat cell damage, degeneration, malignancy, as long as research has been done first

5. A hematopoietic stem cell is used for the treatment of hematological malignancies in bone marrow transplant.

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INA-RESPOND Newsletter

GOOD SCIENCE CAN PRODUCE UNEXPECTED RESULTS: PERSPECTIVE FROM FELLOWSHIP

By: Chuen-Yen Lau, MD, MS, MPH; Christa Zerbe, MD, MS

Chuen-Yen has been working with INA-RESPOND for several years and recently completed an Infectious Disease fellowship. She and Christa Zerbe, director of the NIH Infectious Disease Fellowship Program, have been reflecting on how training experiences shape our perception of research results. Chuen-Yen and Christa were part of a "required" quality improvement (QI) project team that produced unexpected results. This article highlights some of their reflections that are relevant to research in general, including INA-Respond projects.

In a nutshell:

To satisfy the American Council of Graduate Medical Education's requirement that each fellow complete a QI project as part of their training, our institution's Infectious Diseases fellows did a group antimicrobial stewardship project. An increase in use of injudicious antibiotics was noted after the project intervention. This unexpected result engendered an emotional struggle and concerns about how to handle changes in the electronic health record system that had been made as part of the project. Through exploration of scientific factors as well as personal perspectives, the fellows achieved insight on the value of unexpected findings that will undoubtedly influence their future careers.

What a surprise!

After more than a year of preparation and careful collection of data, we were stunned by the results of our primary analysis. We were scheduled to present our fellowship quality improvement (QI) project to the department faculty in two weeks. And then the project was slated to receive an award from hospital leadership for its positive impact on patient care. My co-fellow commented, "These are terrible results. Maybe we shouldn't present these findings or accept the award."

American Council of Graduate Medical Education Quality Improvement (QI) Requirement:

The project had been conceptualized to satisfy the American Council of Graduate Medical Education's requirement that each fellow complete a QI project as part of their training. The QI project had to provide experiential learning to develop "the ability to identify and institute sustainable systems-based changes to improve patient care."[1]

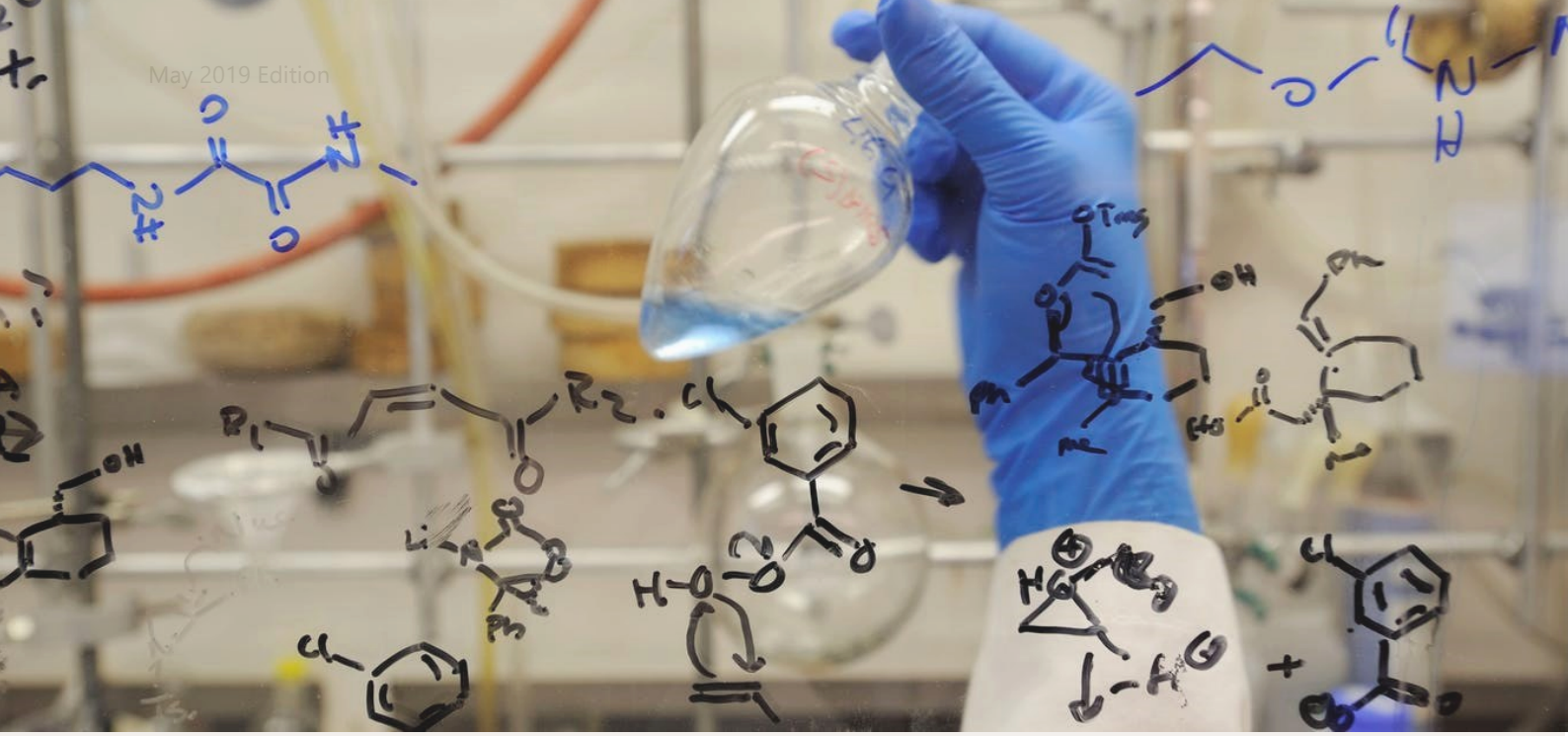
Dr Chuen-Yen Corey Lau—

NIAID (National Institute of Allergy and Infectious Diseases)

Our class of fellows elected to take on a group QI project. We reasoned that a group project would be better than individual projects because 1) we could do a project of larger scope by sharing the workload and thereby have a larger impact; 2) the different perspectives within our fellows' collaboration would result in a larger breadth of insight; and 3) a shared project might be more realistic in light of our other research and curricular commitments.

Our Antibiotic Time Out Project:

We decided on an antimicrobial stewardship project that would reduce injudicious use of antibiotics most likely to generate resistance and increase utilization of the ID consult service. We sought to develop a "time-out prompt" that would pop up in the electronic health record (EHR) if a patient had been on an antibiotic of concern for at least 48



hours. A prescriber would have to acknowledge the alert and select an option indicating their planned course of action before continuing to use the EHR for that patient. We hypothesized that the prompt would reduce injudicious use by 5-20% based on our review of the current literature. However, our results showed no significant change in use of the antibiotics of interest before the prompt compared to after the prompt. Furthermore, there was a disturbing 50% (10% pre-prompt versus 15% post-prompt) increase in antibiotic use considered injudicious.

Some of the fellows were mortified by these unexpected findings. Great anxiety about presenting our results was expressed. Emotions of shame, embarrassment and mediocrity arose. How could we have gotten these results if we had done the project correctly? Was our prompt causing harm? Should we tell the institution to remove the prompt from the EHR immediately?

Were these Bad Results?

Subsequent discussions were extremely valuable, both from a scientific as well as a psychological perspective. We examined project methodology, external factors, potential biases and possible explanations for our findings, which led to edifying insights. The presentation went remarkably well. Illuminating discourse with the staff engendered plans to improve the prompt by modifying its timing, adding microbiology information, expanding the list of antibiotics that could trigger the prompt, requiring provision of indication, obtaining additional user feedback and tailoring electronic post-prompt actions by response and provider. It was even suggested that the next fellowship class build upon this outcome by improving the prompt as their QI project.

Our team found that questioning results is helpful no matter what they show. Data may not conform to expectations. Fortunately, unexpected results are also useful. While we abstractly recognize that negative findings can be valuable, a concrete desire for "positive", "more publishable" findings often dominates. We must remind ourselves that properly conducted research may not produce desired or anticipated results.

Building on Unexpected results:

Our self-esteem restored and anxiety ameliorated, we will shortly accept the award for our fellowship QI project. However, the most valuable outcomes from our QI project are the take-away lessons that will contribute to our effectiveness as researchers and clinicians. We will be more able to optimize design of future projects and effectively interpret research findings.

The EHR antibiotic prompt remains a work in progress that will hopefully improve antimicrobial stewardship at our institution. Perhaps another group of fellows will have more supportive data in the future. In the meantime, this group of infectious disease fellows will apply their QI lessons to their developing research agendas.

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INA-RESPOND Newsletter

COMIC CORNER: YOU JUMP, I JUMP– HMM… MAYBE NOT

By: Aly Diana

Teamwork ability has been evaluated in almost every job interview in the last two decades, and the evaluation method is becoming more and more detailed. Back then, every job applicant was always reminded to avoid the one-person show, and then they also taught this to the college freshmen – to continually work hand-in-hand with the team members. This definition is miss-interpreted and resulting in members pointing at someone who tries to navigate the team or do a different task as bossy or not a team player.

Before jumping into a conclusion, we should understand the definition of a team. A team is a collection of people who interact with each other regularly and are dependent on each other for the attainment of common goals. A team brings together people with different expertise and thus enables the application of specialized knowledge in solving problems. Team building or teamwork helps in improving organizational effectiveness and efficiency.

Teamwork itself has been redefined several times. Most companies assess teamwork ability inseparable from leadership ability because the team should move toward one direction to achieve the goal. Again, every member has their expertise and position according to the skill and knowledge they have and need for the team. If everyone has the precise same task, no one will point where to go, and then the team will be idle. A good team needs a leader who could navigate the team and communicate the strategy to every member, as well as team members who understand each other very well to the extent where great soccer team knows who would receive the ball next and whom it will be passed on without shouting to each other on the field.

The question is who should be the captain? Should the eldest be the captain so he can lead the team? Who will fill which position – based on what? Each member has their own role/function that should not be seen as defining social status. Each role/function with its pre-defined (ground) rules must be filled in to make the team complete thus able to perform to reach the goal.

The sports world is naturally very competitive, so do business/research world with so many things on the stake (credibility, track records, funds). This is why the importance of teamwork has evolved so fast, as better teamwork always means better performance. Therefore, an institution should do whatever it takes, including changes in structure and mindset to build a strong strategic partnership for achieving its goals. Unfortunately, it is still a considerable challenge for conservative institution or profession to appreciate the core concept of teamwork. Just add a sprinkle of willingness to learn and remove the ego. Every person has a different role in bringing the team/institution to a better state, and the success of a team member should be considered as a success of the whole team.

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INA-RESPOND Newsletter

SORE TODAY, STRONG TOMORROW

By: Edrick Purnomo Putra

Have you ever heard of the term "no pain, no gain"? Have you ever experienced muscle soreness a day after a hard work out session? The correct terminology for this type of delayed soreness is delayed onset muscle soreness (DOMS). DOMS is an unpleasant sensation of dull pain on specific muscles after vigorous or unaccustomed exercise that occurs 12 to 48 hours post-exercise and may last for five to seven days. DOMS is an inflammation reaction of the body due to damages on the muscles and its surrounding tissues. Symptoms may vary from weakness on the affected muscle group, stiffness, limitation on the range of motion, and pain. Pain may be felt while the muscle is resting, moving, or when pressure is applied to the tissue. The degree of pain also varies from just a light unpleasant sensation on the muscle to agonizing pain.[1,2]

As we know, sedentary behavior is an obvious problem in our society. In a WHO report on Global Health Risks in 2009, physical inactivity is the fourth leading cause of death with a total of 3.2 million deaths worldwide. It increases the risk of cardiovascular disease, high blood pressure, diabetes, obesity, lipid disorders, depression, anxiety, and even some types of cancer.

Meanwhile, studies show that exercise gives many benefits for physical and mental health. It prevents heart diseases, osteoporosis, diabetes, obesity, and depression. In spite of the known harmful effects of sedentary behavior and physical inactivity, people are still reluctant to exercise. A lot of reasons may come up when someone is asked to change their lifestyle, from time unavailability to lack of enthusiasm (or laziness). Some people are also unwilling to do exercise because they do not want to feel exhausted or suffers from DOMS after exercise. While it might be true that DOMS may impair our daily activity for a certain period, the fact is every single person in this world has suffered from DOMS for at least once in their life. Therefore, it is not something new. Even a trained athlete might also have DOMS when they increase their training intensity or try a new training method.

A lot of research about the cause of DOMS were conducted but gained no visible results. Researchers also put a lot of attention in finding the best way to recover from DOMS yet no satisfactory result was achieved. Why does DOMS matter so much that researchers put a lot of energy to find the best cause and cure for it, even though we know by now that it will go away by itself after a few days? For elite athletes and non-athletes, DOMS is not something we expect. Elite athletes' performance, which is highly anticipated and worth a lot of money, will be impaired by DOMS, and it will also disturb their training regime. DOMS will also make a person reluctant to do exercise, and it will decrease the productivity of workers due to the pain that will disrupt their daily movement.[3]

So, who is the culprit that causes DOMS? Many theories were proposed, and the oldest theory is the lactic acid theory. This theory stated that the lactic acid built up in the muscles would cause the pain. However, the fact that lactic acid will get back to the baseline an hour after exercise makes this theory irrelevant to DOMS.[2,3] Another theory stated that DOMS is caused by a tonic spasm in the muscle motor unit. When the muscle contracts from heavy exercise, ischemia happens in some parts of the muscle, and it causes pain. Pain also causes tonic contraction reflex on the muscle, and it triggers spasm on the motor unit. The spasm itself worsens the ischemia, and the cycle of spasm and ischemia goes on and produces more pain. However, this theory is not proven by electromyography; thus, this theory is stated to be left out.[2]

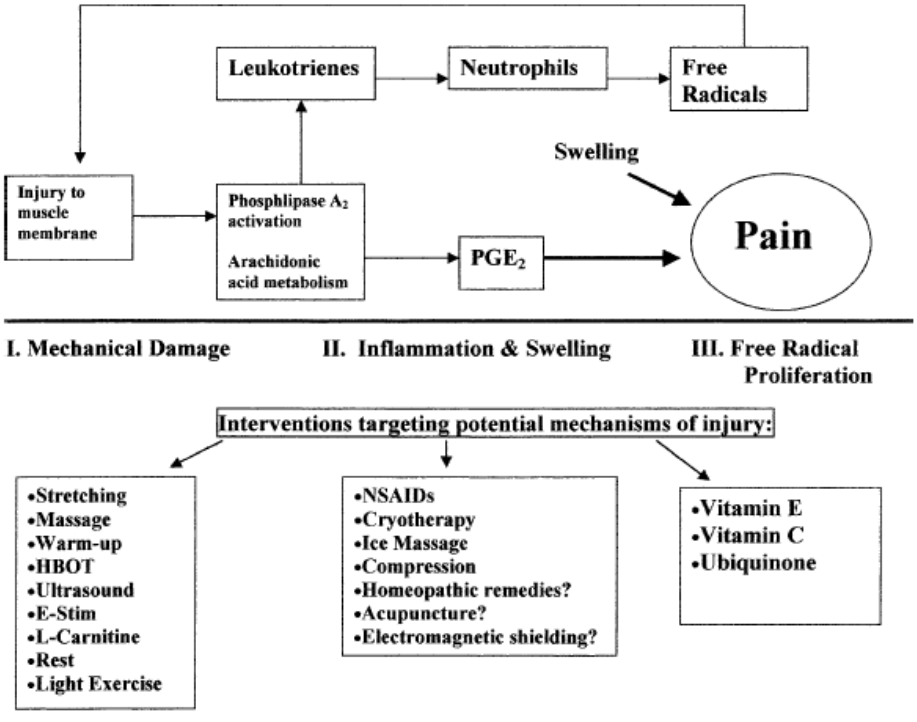

Figure 1. Mechanism of DOMS and its various modality of intervention.[4]

When the muscle contracts, microscopic tears happened mechanically on the muscle, especially from eccentric contraction. Muscle contraction, while the muscle is lengthening on eccentric contraction, causes damage to the sarcomere and muscle fibers. Studies show that increased plasma creatine kinase is usually detected in blood as an indicator of muscle damage. These micro tears trigger inflammation and edema that cause pain. Another theory also stated that micro tears also happen in the connective tissues and tendon. This explains why the pain usually starts on the area around the tendon at the end of the muscle and later spreads to the whole muscle. The breakdown of the collagen of the connective tissue release a protein called hydroxyproline that can be detected in the blood and urine.[2,3]

Other theory stated that DOMS is more than just mechanical damage. This theory emphasizes that the imbalance of ions and enzymes is the cause of the pain. The muscle membrane damage that happens during heavy exercise disrupts the calcium ion balance. Intracellular calcium ions activate the phospholipase enzyme, and that changes phospholipid into arachidonic acid and induces inflammation reaction. By activating the arachidonic and COX cascade, inflammation mediators are released, and it causes edema and pain. Leukotrienes are also released, and it acts as a chemoattractant to neutrophils that releases cytotoxic substances and free radicals or reactive oxygen species (ROS). By looking at all these theories, it seems like more than one mechanism happen simultaneously in causing DOMS.[4,5]

With the known mechanisms of DOMS so far, then the major question is, how do we prevent and treat it? Many interventions have been studied yet they cannot pinpoint one definitive intervention to treat it. Pre and post exercise stretching, the oldest method still used until today to prevent DOMS, fails to prove its benefits on reducing DOMS based on studies, no matter what kind of stretching was studied. Stretching can even worsen DOMS by exacerbating the tears that already happened.[3,6] Other methods such as ultrasound, electrostimulation, homeopathy, and many other trivial substance or supplements are not satisfactory to prevent or attenuate DOMS according to studies.[2,3,7]

Massage is one of the most studied methods to treat DOMS. Studies show the benefits of the application of massage after an exercise. Calcium ion influx and disruption of calcium ion homeostasis may be restored by increasing the blood flow to the affected muscle which can be achieved by massage. This increased blood flow also hinders the margination of neutrophils and reduce prostaglandin production, thus reducing overall inflammation process. Increasing the oxygen delivery helps mitochondria to replenish ATP and facilitates the active transport of calcium in the sarcoplasmic reticulum. Massage also improves the lymph flow which helps in reducing edema. Massage also used as a relaxation method that reduces cortisol and increases endorphin, dopamine, and serotonin. Therefore, it helps to alleviate the pain.[7–9]

Although the pain makes us reluctant to move, passive recovery or total rest is not recommended. Active recovery or light exercise is one of the best ways to alleviate DOMS as it produces a temporary analgesic effect by doing lower intensity exercise or exercising the other part of the body other than the affected muscle. Exercise will increase endorphin release, increase blood flow and break adhesions in the muscle that happened during DOMS thus reducing the pain.[1,2,5,7] Cryotherapy is one of the most popular methods of recovery that is also used to prevent DOMS. Cold water immersion lowers the temperature and causes the vessels to constrict thus reduces edema and halts the inflammation process. In spite of the unclear benefit of cold therapy in reducing DOMS according to research, it is still better than passive recovery.[3,7] Compression garments are also proposed as a method to reduce DOMS. Continuous compression may have benefits in reducing edema and promote recovery although further studies are still needed.[2,7]

As many inflammation processes occur in DOMS, the use of nonsteroidal anti-inflammation drugs (NSAIDs) is also examined. Although NSAIDs may help in reducing inflammation and pain temporarily, the use of NSAIDs to prevent or treat DOMS is not encouraged for its potential abuse. The side effects and chronic overuse effects of NSAIDs should be taken into consideration since its harms outweigh its benefits.[2–5] The involvement of free radicals in DOMS mechanism also rationalizes the use of antioxidants in treating DOMS. Studies show that the supplementations of vitamin C, E, and ubiquinone give benefits in reducing DOMS.[2,4] Supplementations of protein and amino acids, such as BCAA, also provide good results as protein and amino acids are used in protein synthesis. Therefore, it hastens the recovery of muscle function.[3]

So, should we be afraid of DOMS after an exercise? Exercise-induced muscle damage (EIMD) is a mediator of muscle hypertrophy which is needed as a form of physiological adaptation to make us stronger and perform better in the next exercise. Hence, DOMS might be a gross indicator of EIMD although it may vary depending on the individuals since pain or soreness is subjective.[10] Moreover, DOMS is something self-limited and many recovery methods can be done to alleviate it. As time goes by and our body is more accustomed to exercising, the possibility for DOMS to happen will decrease. DOMS can be avoided by starting with moderate intensity exercise and increasing the intensity gradually every one or two weeks. Therefore, there is no excuse to be afraid of experiencing DOMS after exercise since it will make us stronger and healthier in the future. Exercise should be enjoyable and not painful as long as we do it right.

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