

A BRIEF REVIEW ON CRYOGUN MACHINE FOR PRE-CERVICAL CANCER HEALING

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Abstract

Cervical cancer is generally found in women of all ages due to virus infection on epithelial cells of female cervix. It is known that a certain type of Human Papilloma Virus (HPV) is suspected to cause cervix cancer in women from various ethnics. Several therapies have been used to cure cancer diseases like cone biopsy, laser treatment, electrosurgical excision, thermocoagulation, ablation therapy, and cryotherapy. This paper has highlighted on the role of cryogun machine applied in cryotherapy for pre-cervical cancer treatment in relation to freezing technique using liquid nitrogen to kill cancer cells on infectious area.

Keywords: Cervix cancer, Cryogun machine, Cryotherapy

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1. Cancer Disease

Cancer has recognized as malignant disease related to uncontrollable cell splitting and propagating to adjacent cell tissues. Moreover, the disease may attack to other tissues via cell growth causing serious damages of tissues. The malicious cell growth is due to a damage of DNA triggering genes mutation corresponding with cell splitting. Cell mutation may occur due to certain chemical or physical agent known as carcinogen. Cancer disease may show with different symptoms depends on level of malignancy, characters of cell splitting or metastasis effect.

Cancer may cause fatalistic death particularly in many developing countries. However, earlier detection of the symptom can handle cancer disease. Nevertheless, cancer has still remarked as horrible disease until today. Up to date, the main cause of cancer is still unknown.

2. Cervix Cancer

Cervix cancer is commonly found as the third cancer disease. Cervix cancer begins with virus infection destroying epithelial cells of vital female organ. According to level of mortality cervical cancer is in the second order after breast cancer. However, in many developing countries this type of cancer has placed in the first order causing death of women in their reproductive period. Moreover, Marton [1] reported 80% pre-cervix cancer cases found in undeveloped countries.

Furthermore, about 90% cervix cancer found in low-income society and undeveloped countries with less screening program and minimum HPV vaccination [2]. Almost every year more than half million women have undergone cervical cancer and resulted about 300 000 death cases all over the world [3]. However, most of this type of cancer can be prevented if earlier symptom is promptly detected and cured.

3. Cryotherapy

Several therapies are done to treat cervical cancer. Cone biopsy is known as treatment for cone removal where a layer of cervix tissue suspected an abnormality in cone form is removed. Laser treatment applied narrow laser wavelength to kill cancer cells by laser light exposure on suspected infectious area. Loop electrosurgical excision is a method to remove cancer cells from cervix applying electrical cable acting as sharp knife to cut cancel cells. Hysterectomy is a treatment method to discard large part of tissues from cervix and uterus. Cryotherapy is a medical treatment by freezing and killing cancer cells in suspected area. This study has interested in cryotherapy as the topic of the article because cryotherapy has effectively assumed for curing pre-cervical cancer.

Furthermore, cryotherapy is a medical method in order to destroy abnormal tissues in cervix area applying very low temperature. Cryotherapy applies a device namely cryogun for pre-cervical cancer

remedy. During the treatment process, the cryogun is adhered to abnormal cervix area for several minutes. The cryogun will flow low temperature nitrogen liquid through cryogen probe. The low temperature nitrogen liquid will freeze cervix cancer cells and kill the cells [4].

The destroying of cancer cells during the process of cryotherapy implicated with intricate mechanism related to direct and indirect effects. The direct effect implies with intracellular and extracellular states of ice crystals retarding membrane cells, causing dehydration in cells, changing electrolyte concentration, causing enzyme malfunction and protein denaturation, and liquefaction resulting cell emptiness, swelling and cell breaking namely cell thermal shock. The indirect effect implies with vascular change causing ischemic necrosis of tissues and affects body resistant yielding cells damage through mechanism of immune cell toxicity [5].

Nowadays, the cryotherapy method takes benefit from the properties of nitrogen liquid that it can decrease the temperature until -50°C . This condition causes the death of body cell tissues or called as frost bite. When the cell tissues undergone frost bite the treatment to remove cancer cells is much easier [6]. The cryogun device can do this kind of treatment. Table-1 listed the development of cryotherapy with regard to kind of technique and result of cryotherapy treatment ([7] – [36]). Moreover, Table-1 shows that cryotherapy has broad sense of applications related to medical therapy mostly used for oral therapy and cervical management. Up to date, Indonesia has not yet produced this kind of device. In addition, publications in relation to cryotherapy in Indonesia are still a few. Sianturi & Irawati [7] reported a review study on oral cryotherapy in order to reduce oral mucositis. Lestari et al. [8] reported cervix cryotherapy in Indonesia and the results showed that cryotherapy is effective for early management of cervical precancerous lesion. Silaban et al. [9] investigated oral cryotherapy for cancer patients in Indonesia undergoing chemotherapy and found that the therapy achieved successful treatment (75%) regarding no oral mucositis found after chemotherapy. Suwartono & Andrijono [10] investigated the treatment effect of cervical cryotherapy and TCA methods on cervical cancer in Indonesia and the comparison yielded no significant difference. All cryogun devices in Indonesia medical hospitals are coming from abroad. In our knowledge Indonesia has the basic components in order to produce this kind of device. This article attempts to

develop the design of cryogun and therefore, this current study is the strength of this paper.

4. Cryogun Machine

The design of cryogun is built for the purpose of generating low temperature liquid nitrogen. The principal operation in a cryogun based on the Joule – Thomson effect in relation to adiabatic process corresponding with gas expansion through a small opening. The pressurized nitrogen gas flows down through the narrow cryogun tank.

Table-2 listed documents of components used in cryogenic device and reported in patent form([37] – [41]). Only small number of documents presented here and therefore, this is the limitation of this study.

Several important points related to cryogun machine will be described in the following section.

4.1 Basic Operation

The shape of a cryogun is likely a hand gun that has a trigger, which its function is to flow liquid nitrogen until the cryoprobe. Before the liquid nitrogen entered the device, a given size of cryoprobe is pasted to an abnormal cervix area. When the cancer cells get freezing, that part of cervix area is abandoned to liquid. The cryoprobe is abandoned to release spontaneously from the abnormal tissues during liquefaction process. The probe is not allowed to withdraw earlier. According to Cohen [2] and Peter [42], this method needs longer freezing time. When the liquid nitrogen flows to the cryoprobe, it is expected the probe temperature decreased to -50°C so that the part of cervix area infected by abnormality undergone frost bite and the cancer cells dead.

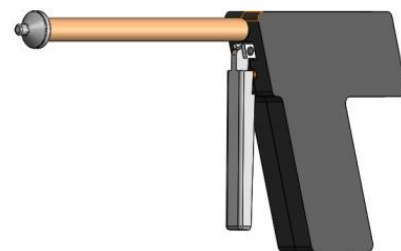


Fig. 1. Cryogun device.

The material used for cryogun machine is varied, it depends on the manufacture brand but usually the basic material is a combination of stainless steel and brass alloy for long life usage. Sometimes polypropylene is utilized to increase stability, while the cover and collar are made of polypropylene for hand insulating.

4.2 Main Components

The cryogun machine is built of several main components. The main components are:

1. Pressure Regulator
2. Main Hose
3. Main Body
4. Trigger Switch
5. Cryoprobe Tip

Pressure Regulator

The function of pressure regulator is to manage the liquid pressure when the cryogun connected to a liquid nitrogen cylinder tank. It should maintain the nitrogen gas under pressure so that the gas can stream down through a small opening to the cylinder tank. The pressure regulator (Fig. 2) simply indicates pressure unit, recorded as kg/cm² or lbs/in², which is divided into three pressure zones. The high zone indicates excessive cylinder pressure or a sign of safety hazard. The middle zone indicates adequate or optimum pressure. The low zone indicates low gas pressure or a sign of inadequate freezing.



Fig. 2. Pressure Regulator

Main Hose

The main hose connected the pressure regulator to the cryogun machine. The function of connecting hose is to transmit nitrogen gas from cylinder tank to cryogun device. It is usually made of polypropylene material to enhance its strength.

Main Body.

In the main body there is a switching mechanism in order to control liquid flow in the cryogun machine. It consists of a hand grip or handle, a trigger for activation, and the cryoprobe tip. Some modified units have the on/off switch for the gas valve that is located in the cryogun.

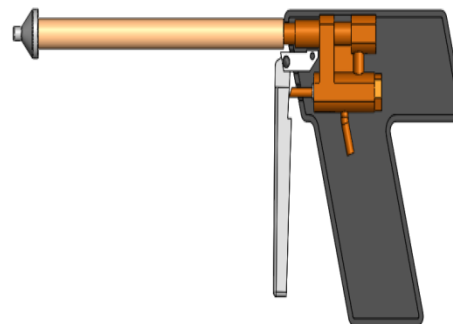


Fig. 3. Main Body

Trigger Switch

The function of trigger switch is to yield forces in switching mechanism in the main body. Activation triggers varied in function. In some modified units, depression of the trigger initiates the freeze, while in others it defrosts the probe tip. Most triggers are in a locked position setting so that the trigger need not be depressed during freezing process.

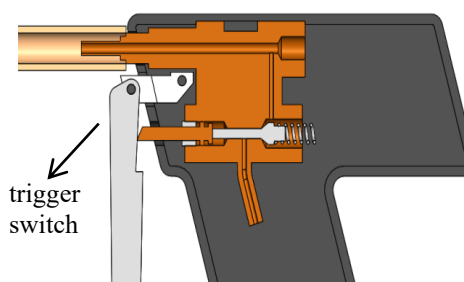


Fig. 4. Trigger Switch

Cryoprobe Tip

The cryoprobe tip is a part of cryogun directly contacted with the abnormal cervix area. The probe tip is made of stainless steel material for safety reason. The probe tip has several shapes depend on its application related to infectious area.

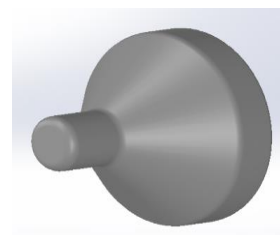


Fig. 5 Probe Tip

Moreover, as the pressurized nitrogen gas reaches the hollow probe tip, the gas rapidly expands, lowering it to a temperature below freezing. Although the probe tip visibly cools, the probe tip has to be maintained as a heat sink. As the probe tip removes heat from cell tissue, the cell tissue gradually cools. Then the infectious cell tissue experiences destruction. The capacity of the probe tip as a heat sink is affected by several factors such as size, material, composition and temperature of the probe tip [8]. According to Fanyi [9], factors such as tissue moistness, extent of tissue contact, freeze duration and gas pressure also influence the heat diffusion.

5. Discussion

Cryotherapy is used to destroy abnormal cells in human body. In many cancer cases, this kind of therapy has not used as the first priority. Nevertheless, cryotherapy will be applied when other kind of treatment is not successful particularly if the recovered cancer case came back after had treated by other therapy.

Nevertheless, cryotherapy is often used to cure either skin cancer or pre-cancer. However, this kind of treatment is used for healing abnormality in some internal organs as liver and cervix in the emergency condition that conventional operation is not possible to be conducted due to other disease problem [6].

In addition, cryotherapy is very efficient from the standpoint of level of recovery and level of operation. A clinical study reported level of recovery of 83% for curing chronics cervix by cryotherapy compared to the same case by electrical cautery (62%) [1]. The comparison is shown in Table-3. On other occasion, Duan [10] reported investigation on pre-cervix cancer using two methods, i.e. thermocoagulation and cryotherapy and the results show no significant difference with respect to vaginal discharge as shown in Table-4.

The process of cryotherapy applying cryogun has some advantages over several factors. The cryotherapy using cryogun is relatively low cost. When large scale production can be managed it can reduce production cost and import tax can be avoided particularly for developing countries. Furthermore, more health institutions may handle the management of pre-cervical cancer treatment. Besides big hospitals can handle cryotherapy, more small clinics in district area may manage this kind of therapy. As a portable device, the cryogun can be carried anywhere even to isolated or remote area. In the forthcoming, an aluminium battery is designed to be applied in this portable device [11]. Nevertheless,

this portable cryogun is still under designing process and needs further assessment to investigate the temperature distribution in the cryogun. Another disadvantage, this device can not kill cancer cells in broader spectrum area [4].

In addition, the role of cryoprobe tip as the component part may affect the operation of cryogun. As already mentioned above, the heat diffusion is influenced by the material and size of cryoprobe tip. A good cryoprobe tip has to be made of a good thermal conducting metal, such as silver, gold, or copper [8]. The interchangeable tips are available in various shapes and sizes to ensure maximum contact of the tip with the infectious cell tissues to be destroyed. Furthermore, the cryoprobe tip must be disinfected by certain chemical disinfectant. Some cryosurgical units are provided with pyrometer to show the real temperature of activated cryoprobe tip. Some pyrometers indicate continuous thermal data. Pyrometer types are available in digital or analog mode. Fig. 6 shows the cryosurgical unit provided with a cylinder tank, pressure regulator, cryogun and cryoprobe tip [8]. As we may see in Fig. 6, the cryogun is the component part of the cryosurgical unit that we discussed in this writing.

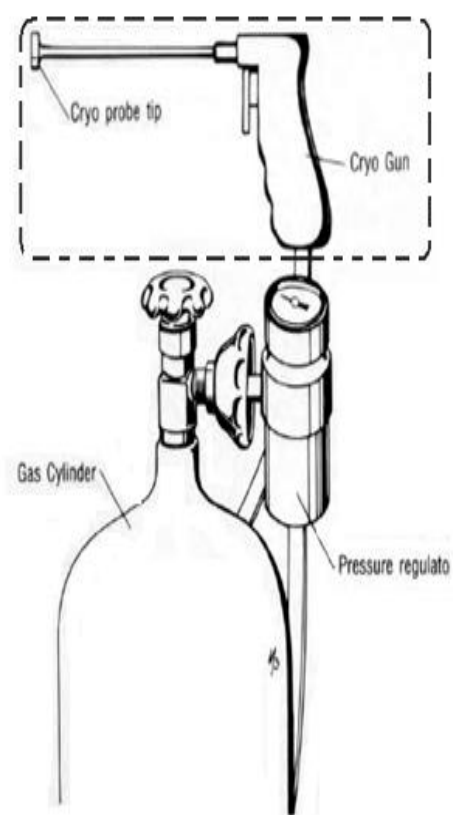


Fig.6. Cryosurgical unit with cylinder tank and pressure regulator. Picture of cryogun and cryo prob tip in bracket sign.

Although cryotherapy has some risk factors, nevertheless, the risk factor is assumed to be lower than other kind of cancer therapy like operation and radiation. The risk factors in relation to cryotherapy included: infection, healthy cell and tissue damage near exposed area, skin abrasion, scarring, sexual malfunction, white spots, loss of sense feeling and painful feeling. Some investigators reported that patients might go home after cryotherapy treatment at the same day, however, there were patients that had to overstay in hospital due to internal organ treatment [6].

Ablation technique in relation to tissues removal has become very popular during last decades such as microdermabrasion treatment using vacuum pressure for skin treatment [12].

6. Conclusions

From the brief discussion mentioned above, the cryogun is a simple machine used for ablation technique corresponding with tissue removal either by vaporation, abrasion, or destruction in cryosurgery. The portable cryogun is still under developing process that will be adapted for many developing countries in the forthcoming application. In addition, the cryogen equipment has positive prospect for cryosurgical treatment especially on the case of pre-cervix cancer remedial.

Up to date, publication reports focused on instrumentation used for cryotherapy are limited. With limited publication numbers, this article reported that most cryotherapy has used for oral mucositis treatment due to chemotherapy and for reducing perineal pain due to childbirth, as well as for cervical cancer treatment. Available reports on cryotherapy in Indonesia are concentrated on oral therapy and cervical cancer through See and Treat approach.

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References

- [1] Marton, V. Shuja, T. Dawood, Sidhom, J.W. & Enriquito, L. Cryotherapy device for maintenance. *Patent US9717546B2_2017_USA*.
- [2] Cohen, P. Jhingran, A. Oaknin, A. & Denny, L. Cervical cancer. *Lancet*. 2019; 393: 169-182.
- [3] Dennis, R.M. & Patrick LePivert. Methods for improved cryo-chemotherapy tissue ablation. *Patent (US20120143167A1_2012_USA)*.
- [4] Catherine, N. & Daniel, B.E. A systematic review on the use of cryotherapy versus other treatments for basal cell carcinoma. *Dermatol. Online J*. 2018; 24(11).
- [5] Yu, C.H. Lin, H.P. Cheng, S.J. Sun, A. & Chen, H.M. Cryotherapy for oral precancers and cancers. *Formos Med. Assoc.* 2014; 113: 272-277.
- [6] Krans, B. Cryosurgery: Purpose, Procedure and Risk – *Healthline*. December 16, 2015.
- [7] Sianturi, E. & Irawati, D. The effectiveness of oral cryotherapy to reduce oral mucositis among cancer patients undergoing chemotherapy: A literature review. *Int. J. Nursing Health Serv.*, 2019; 2(2): 102-109.
- [8] Lestari, L. Purwoto, G. & Nuranna, L. Efficacy and Safety of Cryotherapy in "See and Treat" program in Jakarta primary health centre. *Indones. J. Obstet. Gynecol.*, 2016; 4(4): 227 – 233.
- [9] Silaban, N.Y. Nasution, S.S. & Siregar, C.T. Influences of oral cryotherapy on mucositis prevention in cancer patients with chemotherapy. *Indones. J. Med. Health*, 2020; 11(2): 165-171.
- [10] Suwartono, H. & Andrijono. Efficacy of trichloroacetic acid (TCA) compared to cryotherapy in treating patients with positive IVA result. *Indones J. Obstet. Gynecol.*, 2020; 8(4): 249 – 253.
- [11] Askarifar, M. Lakdizaji, S. Ramzi, M. Rahmani, A. & Jabbarzadeh, F. The effects of oral cryotherapy on chemotherapy-induced oral mucositis in patients undergoing autologous transplantation of blood stem cells. *A clinical trial. Iranian Red Crescent Med. J.* 2016;18(4): e24775.
- [12] Batlle, M. Morgades, M. Vives, S. Ferrà, C. Oriol, A. Sancho, J.M. & Ribera, J.M. Usefulness and safety of oral cryotherapy in the prevention of oral mucositis after conditioning regimens with high-dose melphalan for autologous stem cell transplantation for lymphoma and myeloma. *Europ. J. Haematol.* 2014; 93(6): 487–491.
- [13] Rashad H.M. Effect of cryotherapy on the occurrence of stomatitis induced by chemotherapy among children with bone

- tumors in Egypt. *J. Biol. Agric. Health Care*. 2014; 4(18): 49–58.
- [14] Nawi, R.I.L. Chui, P.L. Ishak, W.Z.W. & Chan, C.M.H. Oral cryotherapy: Prevention of oral mucositis and pain among patients with colorectal cancer undergoing chemotherapy. *Clin. J. Oncol. Nursing*. 2018; 22(5).
- [15] Okamoto, K. Ninomiya, I. Yamaguchi, T. Terai, S. Nakanuma, S. Kinoshita, J. et al. Oral cryotherapy for prophylaxis of oral mucositis caused by docetaxel, cisplatin, and fluorouracil chemotherapy for esophageal cancer. *Esophagus*. 2019;16(2): 207–13.
- [16] Kim. H.J. An, J.W. Lee, Y.Y. Shin, Y.S. The effects of cryotherapy on perineal pain after childbirth: A systematic review and meta-analysis. *Midwifery*. 2020; 89: 102788.
- [17] Beleza, A. C. Ferreira, C. H. Driusso, P. Dos Santos, C. B. & Nakano, A. M. Effect of cryotherapy on relief of perineal pain after vaginal childbirth with episiotomy: a randomized and controlled clinical trial. *Physiotherapy*. 2017; 103 (4): 453-458.
- [18] Francisco, A. A. de Oliveira, S. M. J. V. Steen, M. Nobre, M. R. C. & de Souza, E. V. Ice pack induced perineal analgesia after spontaneous vaginal birth: Randomized controlled trial. *Women Birth*. 2018; 31: e334 – e340.
- [19] Morais, I. Lemos, A. Katz, L. Melo, L. F. R. & Maciel, M. M. Perineal pain management with cryotherapy after vaginal delivery: A randomized clinical trial. *Rev. Bras. Ginecol. Obstet*. 2016; 38: 325 – 332.
- [20] Leventhal, L. C. de Oliveira, S. M. Nobre, M. R. & da Silva, F. M. Perineal analgesia with an ice pack after spontaneous vaginal birth: a randomized controlled trial. *J. Midwifery Womens Health*. 2011; 56(2): 141-146.
- [21] Lu, Y. Y. Su, M. L. Gau, M. L. Lin K. C. & Au, H. K. The efficacy of cold-gel packing for relieving episiotomy pain – a quasi-randomised control trial. *Contemp. Nurs*. 2015; 50: 26 – 35.
- [22] Neto, F. Henriques, A. Amorim, R. Maria, M. Katz, L. Morais, I. Lemos, A. & Leal, N. Cryotherapy for the control of perineal pain following vaginal delivery: A randomized clinical trial. *Obstet. Gynecol*. 2015; 125: 64s – 65s.
- [23] Oliveira, S. M. Silva, F. M. Riesco, M. L. Latorre Mdo, R. & Nobre, M. R. Comparison of application times for ice packs used to relieve perineal pain after normal birth: a randomised clinical trial. *J. Clin. Nurs*. 2012; 21: 3382 – 3391.
- [24] Kalli, K. & Fousekis, K. The effects of cryotherapy on athletes' muscle strength, flexibility, and neuromuscular control: A systematic review of the literature. *J. Bodywork & Movement Therapies*. 2019; 24(2): P175 – 188.
- [25] Rymaszewska, J.E. Stanczykiewicz, B. Lion, K. & Misiak, B. The impact of whole-body cryotherapy on lipid profile: A systematic review and meta-analysis. *Complementary Therapies in Med*. 2020; 55: 102568.
- [26] Adefuye, P.O. Dada, O.A. Adefuye, B.O. Shorunmu, T.O. Akinyemi, B.O. Idowu-Ajiboye, B.O. Feasibility, acceptability, and effectiveness of visual inspection of the cervix with acetic acid and cryotherapy for dysplasia in Nigeria. *Int. J. Gynecol. Obstet*. 2015; 129: 62 – 66.
- [27] Nene, B.M. Hiremath, P.S. Kane, S. Fayette, J.M. Shastri, S.S. & Sankaranarayanan, R. Effectiveness, safety, and acceptability of cryotherapy by midwives for cervical intraepithelial neoplasia in Maharashtra, India. *Int. J. Gynecol. Obstet*. 2008; 103: 232–236.
- [28] Nuranna, L. Aziz, M.F. Cornain, S. Purwoto, G. Purbadi, S. Budiningsih Setya, Budiningsih, S. & Peters, A.A.W. Cervical cancer prevention program in Jakarta, Indonesia: See and Treat model in developing country. *J. Gynecol. Oncol*. 2012; 23 (3):147-152.
- [29] Blumenthal, P.D. Lauterbach, T.M. Sellors, J.W. & Sankaranarayanan, R. Training for cervical cancer prevention programs in low-resource settings: Focus on visual inspection with acetic acid and cryotherapy. *Int. J. Gynecol. Obstet*. 2005; 89: S30 — S37.
- [30] Apriyanti, R. Ernawaty & Nandini, N. Preventing cervical cancer by increasing coverage of visual inspection with acetic acid and cryotherapy in public health centre. 4th International Conference on Tropical and Coastal Region Eco Development. *IOP Conf. Series: Earth and Environmental Science*. 246 (2019) 012064.
- [31] Paul, P. Winkler, J.L. Bartolini, R.M. Penny, M.E. Huong, T.T. Nga, L.T. Kumakech, E. Mugisha, E. & Jeronimo, J. Screen-and-Treat

- approach to cervical cancer prevention using visual inspection with acetic acid and cryotherapy: Experiences, perceptions, and beliefs from demonstration projects in Peru, Uganda, and Vietnam. *The Oncologist*. 2013; 18: 1278–1284.
- [32] Vet, J.N.I. Kooijman, J.L. Henderson, F.C. Aziz, F.M. Purwoto, G. Susanto, H. IGD Surya, I.G.D. Budiningsih, S. Cornain, S. Fleuren, G.J. Trimbos, J.B. & Peters, A.A.W. Single-visit approach of cervical cancer screening: See and Treat in Indonesia. *British J. Cancer*. 2012; 107: 772–777.
- [33] Domingo, E.J. Noviani, R. Md Noor, M.R. Ngelangel, C.A. Limpaphayom, K.K. Thuan, T.V. Louie, K.S. & Quinng, M.A. Epidemiology and prevention of cervical cancer in Indonesia, Malaysia, the Philippines, Thailand and Vietnam. *Vaccine*. 2008; 26S: M71–M79.
- [34] Azar, J.K. Moosazadeh, M. Nesamia, M.B. & Goudarziana, A.H. Effect of cryotherapy on arteriovenous fistula puncture-related pain in hemodialysis patients: A systematic review and meta-analysis. *Complementary Therapies in Medicine*. 2020; 49: 102326.
- [35] Bryczkowska, I. Radecka, A. Knyszynska, A. Łuczak, J. & Lubkowska, A. Effect of whole body cryotherapy treatments on antioxidant enzyme activity and biochemical parameters in patients with multiple sclerosis. *Fam. Med. Prim. Care. Rev*. 2018; 20(3): 214–217.
- [36] Sadaf, D. Ahmad, M.Z. & Onakpoya, I.J. Effectiveness of intracanal cryotherapy in root canal therapy: A systematic review and meta-analysis of randomized clinical trials. *J. Endodontics*. 2020; 46(12): 1811 – 1823.
- [37] Thomas, E. H. Walter, H. H. Robert, M. L. & Raymond, W. M . Cryogenic liquid storage vessel. *Patent US3274788A_1966_USA*.
- [38] Peter, J. L. Alexei, V. B. Robert, D. & Sergey, B. Cryotherapy device. *Patent US7507233B2_2004_USA*.
- [39] Peter, J. L. Alexei, V. B. Robert, D. & Sergey, B. Methods and system for cryogenic cooling. *Patent US8387402B2_2004_USA*.
- [40] Peter, L. Alexei, B. Robert, D. Pramod, K. & Sergey, B. Cryotherapy probe. *Patent US20040215294A1*.
- [41] Daniel, M. L. Cryotherapy temperature monitoring. *Patent US6709431B2*
- [42] Peter, L. Alexei, B. Robert, D. Pramod, K. & Sergey, T.B. Cryotherapy probe. *Patent_US8591503B2_2016_USA*.
- [43] Ferris, D.G. & Ho, J.J. Cryosurgical equipment: A critical review. *J. Family Practice*. 1992; 35(2): 185-193.
- [44] Fanyi, C. Baijie, Z. & Jian, X. Influence of moisture on the insulation characteristics of nitrogen. *J. Int. Council Electrical Eng*. 2017; 8(1): 51-56.
- [45] Duan, L. Du, H. Belinson, J.L. Liu, Z. Xiao, A. Liu, S. Zhao, L. Wang, C. Qu, X. & Wu, R. Thermocoagulation versus cryotherapy for the treatment of cervical precancers. *J. Obstetrics Gynaecology Research*, 2020; 47(1): 279-286.
- [46] Alva, S. Sundari, R. Wijaya, H.F. Majlan, E.H. Sudaryanto, Arwati, I.G.A. & Sebayang, D. Preliminary study on aluminum-air battery applying disposable soft drink cans and Arabic gum polymer. *IOP Conf. Series: Materials Science and Engineering*, 237, 012039, 2017.
- [47] Bagaskara, A. Anggraini, R. & Sundari, R. The performance of microdermabrasion machine based on vacuum pressure drop. *Int. J. Public Health & Health Sci*. 2021 (Accepted).

Table 1. The development of cryotherapy addressing to technique and purpose of therapy in medical application.

Ref.	Author(s)	Technique	Purpose of therapy	Participant	Result of treatment	Country
[7]	Sianturi & Irawati (2019)	Oral cryotherapy using ice chips or ice cold water to the mouth	To reduce oral mucositis due to chemotherapy	Cancer patients undergoing chemotherapy	Oral cryotherapy showed significant treatment effect	Asia and Europe (a review)
[9]	Heydari <i>et al.</i> , 2012	Oral cryotherapy for cancer patients undergoing chemotherapy using ice chips/ ice cold water to the mouth	Oral cryotherapy to reduce oral mucositis due to chemotherapy	80 breast cancer patients	45% succeeded	Iran
[11]	Askarifar <i>et al.</i> , 2016	Oral cryotherapy for patients undergoing stem cell transplantation	To reduce severe oral mucositis due to bone marrow transplantation	29 patients undergoing stem cell transplantation	Cryotherapy showed significant improvement	Iran
[12]	Battle <i>et al.</i> , 2014	Oral cryotherapy for patients undergoing autologous stem cell transplantation	To reduce oral mucositis due to stem cell transplantation	134 patients with lymphoma and myeloma	63 % (85/134)	Spain
[13]	Rashad H.M., 2014	Oral cryotherapy for children using ice cubes to the mouth	To reduce oral mucositis due to chemotherapy	60 children undergoing bone tumor	Oral cryotherapy showed a reduction on children mucositis	Egypt
[14]	Nawi <i>et al.</i> , 2018	Oral cryotherapy for patients undergoing colorectal cancer using ice chips to mouth	To reduce oral mucositis due to fluoro-uracil based chemotherapy	80 patients undergoing colorectal cancer	Significant positive impact on pain relief	Malaysia
[9]	Silaban <i>et al.</i> , 2020	Oral cryotherapy for patients undergoing cancer	To reduce oral mucositis due to chemotherapy	32 cancer patients	75 % (24/32)	Indonesia
[15]	Okamoto <i>et al.</i> , 2019	Oral cryotherapy for patients undergoing esophageal carcinoma	To alleviate mucositis due to DCF chemotherapy	72 esophagus cancer patients	(58/72) succeeded	Japan
[10]	Suwartono & Andrijono, 2020	Cervical cryotherapy for patients with VIA positive	To compare between cervical cryotherapy and trichloroacetic acid (TCA) methods on cervical cancer patients	36 VIA positive patients for cervical cryotherapy and TCA methods, respectively	97.2 % with respect to cervical cryo and TCA (no significant difference)	Indonesia
[16]	Kim <i>et al.</i> , 2020	Cervical cryotherapy for perineal pain after childbirth by introducing ice packs or gel packs to vagina	To relieve perineal pain in women after child birth	1492 women after childbirth	No significant difference between ice packs or gel packs	Korea
[17]	Beleza <i>et al.</i> , 2017	Cervical cryotherapy for vaginal pain after childbirth with episiotomy using crushed-ice backs	To relieve vaginal pain due to childbirth with episiotomy	50 women after childbirth with episiotomy	88% women satisfied	Brazil
[18]	Francisco <i>et al.</i> , 2018	Cervical cryotherapy using plastic ice packs	To alleviate perineal pain after spontaneous vaginal birth	69 women after spontaneous childbirth	Perineal pain decreased 30 % after immediate cryotherapy	Brazil

[19]	Morais <i>et al.</i> , 2016	Cervical cryotherapy using latex glove with crushed ice	To manage perineal pain management after vaginal delivery	80 women after childbirth	No significant difference of using cryotherapy vs no localized cooling	Brazil
[20]	Leventhal <i>et al.</i> , 2011	Cervical cryotherapy using frozen water pack	To reduce perineal pain after spontaneous vaginal delivery	76 women after vaginal birth	Significant reduction of pain after 20 minute treatment ($p < 0.001$)	Brazil
[21]	Lu <i>et al.</i> , 2015	Cervical cryotherapy applying cold gel packing	To manage perineal lesion after vaginal birth with episiotomy	70 women after childbirth	Significant reduction of pain at 48h postpartum	Taiwan
[22]	Neto <i>et al.</i> , 2015	Cervical cryotherapy applying crushed ice packs to perineal region	To control perineal pain and vaginal edema after vaginal birth		No adverse effect applying cryotherapy (95% confidence)	Brazil
[23]	Oliveira <i>et al.</i> , 2012	Cervical cryotherapy applying ice packs to perineal region	To relieve perineal pain after normal childbirth	38 women at postnatal	72.8 % reported pain relief	Brazil
[24]	Kalli & Fousekis, 2019	Cryotherapy for muscle strength studies: (i)cold water immersion (n = 13); (ii) ice packs (n = 7); (iii) cold water pressure machine (n = 2); (iv) cold chamber (n = 1)	To investigate effects of cryotherapy on muscular strength and flexibility of athletes	23 athletes	Positive impact of cryotherapy is improving joint flexibility. Four cryo techniques are not significantly different in terms of muscular strength.	Cyprus and Greece
[25]	Rymaszewska <i>et al.</i> , 2020	7 studies selected from 956 publications of WBC related to extremely low temperatures divided into two cryo chambers: (i) -10°C to -60°C and (ii) -120°C to -160°C).	Impact of whole body cryotherapy (WBC) on lipid profile	189 adult participants (159 males and 30 females)	WBC significantly reduced cholesterol, LDL (low density lipoprotein) and triglycerides	Poland
[26]	Adefuye <i>et al.</i> , 2015	Cervical cryotherapy for abnormality growth using freezing probe, cervical smear and colposcopy.	To demonstrate VIA technique followed by treatment of dysplasia with cryotherapy	127 women undergone cervical cryotherapy	121 (95.3%) showed negative result after one year	Nigeria
[27]	Nene <i>et al.</i> , 2008	Cervical cryotherapy for cervical intraepithelial neoplasia using ablative treatment	To train midwives in rural area to demonstrate cervical cryotherapy	1068 women undergone cervical cryotherapy	Minor adverse effects only found for 5.2%	India
[29]	Blumenthal <i>et al.</i> , 2005	Integrated treatment of VIA, VILI and cryotherapy	To train nurses and doctors for cervical treatment in Alliance for Cervical Cancer Prevention (ACCP) program	119 physicians and 47 non physicians trainee	The ACCP training is necessary for service-delivery conditions	USA

[28]	Nuranna <i>et al.</i> , 2012	Intergrated treatment of VIA and cryotherapy in See and Treat model.	To demonstrate cryotherapy for VIA positive patients	2216 trainee: (641 doctors, 678 midwives, 610 public health and 278 key people from society)	See and Treat model is promising for screening and treatment of precancerous lesions.	Indonesia
[8]	Lestari <i>et al.</i> , 2016	Integrated procedure of VIA followed by cervical cryotherapy in terms of age and number of marriage, smoking habit and contraception.	To evaluate the efficacy and safety of cervical cryotherapy	86 women participants	90.70% success in See and Treat program	Indonesia
[30]	Apriyanti <i>et al.</i> , 2019	Integrated treatment of VIA followed by cervical cryotherapy	To increase recommendation on VIA coverage and cervical cryotherapy	350.979 woman in reproductive-age followed cervical cryotherapy	35.55% success in See and Treat program	Indonesia
[31]	Paul <i>et al.</i> , 2013	Integrated management of VIA coverage and cervical cryotherapy in See and Treat program	To evaluate See and Treat approach in three countries based on belief, perception and experience	25 women (Peru), 21 women (Uganda), 12 women (Vietnam)	Obstacles: (i) lack of cryotherapy facilitations and machine problem; (ii) limited number of trainee providers; (iii) multiple channel bureaucracy.	Peru, Uganda, Vietnam
[32]	Vet <i>et al.</i> , 2012	Integrated management of VIA, histology and cryotherapy in See and Treat program	To evaluate See and Treat program	918 women with VIA positive received cryotherapy	See and Treat program is necessary to reduce cervical cancer	Indonesia
[33]	Domingo <i>et al.</i> , 2008	Integrated management of pap smears, VIA, colposcopy and cryotherapy based on age, parity and sexual partner.	To evaluate cervical cancer management in ASEAN countries based on young age, high parity and multiple sexual partners.	Cryotherapy: 200 women (Indonesia), women with HPV (Malaysia, Vietnam and Thailand), 195 women (The Philippines).	Cervical cancer program in ASEAN countries at that moment not yet raised to target achievement due to high cost management and limited facilities.	Indonesia, Malaysia, The Philippines, Thailand, Vietnam
[34]	Azar <i>et al.</i> , 2020	Cryotherapy by placing ice packs between the thumb and index finger into fistula area	To reduce fistula related pain in rectum area due to hemodialysis	422 hemodialysis patients	Positive effect of cryotherapy on arteriovenous fistula puncture-related pain	Iran
[35]	Bryczkowska <i>et al.</i> , 2018	Whole body cryotherapy using low chamber temperature – 130°C	To treat patients with multiple sclerosis based on biochemical parameter.	30 women undergone multiple sclerosis	84 % success in treatment of complex neurological diseases.	Poland

[36]	Sadaf <i>et al.</i> , 2020	Intracanal cryotherapy using cold saline irrigation as final irrigant	To reduce root canal pain due to dental operation	810 patients with pulpal pathosis undergoing root canal therapy	Significantly reduced root canal pain at 6 - 24 h after intracanal cryotherapy.	England (a review)
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Note: VIA = visual inspection with acetic acid; VILI = visual inspection with Lugol's iodine; RCT = randomized controlled trial; DCF = docetaxel-cisplatin-fluorouracil; HPV = High-risk human papillomavirus

Table 2. Instrument and its components used for cryotherapy

Ref.	Inventor	Component	Specification	Document type
[37]	Thomas E H, Walter H H, Robert M L, Raymond W M	Cryogenic liquid storage vessel	Vessel without pressure provided by thermal insulation, e.g. Dewar flask	Patent US3274788A 1966
[38]	Peter J L, Alexei V B, Robert D, Sergey B	Cryotherapy device	A cryotherapy device provided with multiple cryoprobes, each of which has a shaft with a closed distal end adapted for insertion into a body for flowing cryogenic fluid through shaft to reduce temperature.	Patent US7507233B2 2004
[39]	Peter J L, Alexei V B, Robert D, Sergey B	Methods and system for cryogenic cooling	Provided for cooling object with a cryogen having critical pressure and critical temperature. A pressure of the cryogen is raised above a pressure value determined to provide the cryogen at a reduced molar volume that prevents vapor lock.	Patent US8387402B2 2004
[40]	Peter L, Alexei B, Robert D, Pramod K, Sergey B	Cryotherapy probe	Probe design for gas-based cryotherapy adapted for using in the body.	Patent US20040215294A1
[41]	Daniel M L	Cryotherapy temperature monitoring	Apparatus for temperature monitoring in cryotherapy	Patent US6709431B2
[1]	Marton V, Shuja T, Dawood, John W S, Enriquito L	Cryotherapy device for maintenance	Cryotherapy device for treatment of cervical precancerous lesion	Patent US9717546B2 2017

Table 3. Data of cervix cancer recovery between cryotherapy and diathermy cauterization

Mode of treatment and total number of patients	Number of patients with completely healed cervix					Cervix not healed at 12 weeks
	At 4 weeks	At 6 weeks	At 8 weeks	At 10 weeks	At 12 weeks	
Cryosurgery 52 patients	7 (13 %)	33 (63 %)	37 (71 %)	41 (79 %)	43 (83 %)	9 (17 %)
Diathermy Cauterization 50 patients	4 (8 %)	23 (46 %)	25 (50 %)	29 (58 %)	31 (62 %)	19 (38 %)

Source: Marton et al. (2017).

Table 4. Thermocoagulation treatment compared to cryotherapy addressing to pre-cervix cancer.

Group	Vaginal discharge			Vaginal bleeding		
	No. women (%)	Start time, days	Duration, days	No. women (%)	Start time, days	Duration, days

Thermocoagulation	69 (100)	1	17.2 ± 6.9	54 (78.3%)	10	10.6 ± 5.8
Cryotherapy	70 (100)	0	20.8 ± 6.5	17 (24.3%)	7	5.6 ± 3.2
p-value	1.000	0.029	0.002	< 0.001	0.149	0.001

Note: values as mean ± standard deviation.

Source: Duan et al. (2020).