

Effectiveness and Determinant Factors of Successful *Scalp Cooling* in Preventing *Chemotherapy Induced Alopecia* in Breast Cancer Patients : Literature Review

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ABSTRAK

Latar Belakang: *Chemotherapy induced Alopecia* (CIA) merupakan salah satu gejala yang paling dikeluhkan dan menyebabkan tingginya tingkat stress pada pasien kanker payudara. *Cryotherapy* atau *Scalp Cooling* merupakan salah satu alternatif untuk menurunkan metabolisme obat kemoterapi yang ada pada folikel rambut dengan memberikan suhu dingin yang diberikan pada kepala pasien. terbatasnya artikel atau jurnal yang membahas tentang keefektifan dari pemberian *Cryotherapy* pada pasien.

Tujuan: mengidentifikasi pengaruh *Cryotherapy* terhadap pencegahan *Chemotherapy induced Alopecia* pas pasien kanker payudara dan faktor yang menentukan kesuksesan dalam pemberian *Cryotherapy*.

Desain: Studi Literatur

Data : pencarian literatur menggunakan Ebscohost, Scopus, Science Direct, and ProQuest database dari tahun 2009 sampai dengan 2019.

Metode: pengumpulan dan proses analisis artikel menggunakan *CASP*.

Hasil: dari 278 artikel yang ditinjau menggunakan *CASP*, terdapat 10 artikel yang memenuhi kriteria inklusi. Total responden dari 10 artikel yang digunakan sebanyak 1201 pasien kanker payudara yang sedang menjalani kemoterapi. Seluruh artikel yang digunakan dalam studi ini menunjukkan dampak yang positif dalam menurunkan tingkat keparahan alopecia pada pasien kanker payudara. Evaluasi yang digunakan menggunakan kebutuhan pasien dalam menggunakan penutup kepala, tingkat rambut yang rontok, pertumbuhan rambut, terdapat beberapa efek samping yang ditimbulkan dalam pemberian *cryotherapy* pada pasien antara lain sakit kepala, kedinginan, mual.

Kesimpulan:

Cryotherapy secara signifikan dapat menurunkan tingkat keparahan alopecia pada pasien kanker payudara dengan menghambat proses mitosis dan vasokonstriksi pada kepala. Terdapat beberapa faktor yang harus dipertimbangkan dalam pemberian *cryotherapy* antara lain jenis alat yang digunakan, durasi pemberian, suhu, dosis dan jenis obat kemoterapi yang digunakan. Untuk penelitian selanjutnya, perlunya mempertimbangkan beberapa faktor yang mempengaruhi keberhasilan *cryotherapy* untuk pasien dan respon pasien selama pemberian

Kata-kata Kunci : *Breast Cancer, Chemotherapy Induced Alopecia, Cryotherapy, Scalp Cooling,*

ABSTRACT

Background: *Chemotherapy induced Alopecia* (CIA) is one of the most complained and cause the highest distress in breast cancer patients with chemotherapy. *Cryotherapy* or *Scalp Cooling* is an alternative intervention to reduce metabolism of cytotoxic agents against hair follicle by lowering the temperature of the scalp. Literature that discusses the effectiveness of *Cryotherapy* in breast cancer patients is still limited.

Objective: Summarize and investigate the effect of *Cryotherapy* on preventing *Chemotherapy induced Alopecia* in breast cancer patients and its determinant factors of successful *Cryotherapy*.

Design: Literature Review

Data Sources: A search was performed by using Ebscohost, Scopus, Science Direct, and ProQuest database from 2009 to 2019 for research article.

Review methods: A systematic process was used to analyze and extract data include studies using *CASP*.

Result: From 278 articles that have been observed using *CASP*, only 10 articles match the inclusion criteria. Total respondents in 10 articles were 1201 breast cancer patients undergoing chemotherapy. All articles used in this study showed positive results about the effect of *Cryotherapy* on decreasing the severity of *Chemotherapy Induced Alopecia* (CIA) measured by hair preservation, hair loss, hair regrowth, and decreasing use a wig or head covering. The importance of continuously monitoring the patient's condition to manage the side effects caused by *Cryotherapy* such as headaches, cold, and nausea.

Conclusion:

Cryotherapy significantly reduce the severity of CIA by inhibit the process of mitosis and vasoconstriction. There are several factors that must be considered when giving *Cryotherapy*, such as type of chemotherapy, dosages, device, duration of administration, and temperature. For further research, it is important to considered some factors that can affect the successful of *Cryotherapy* and the patient response

Keywords : *Breast Cancer, Chemotherapy Induced Alopecia, Cryotherapy, Scalp Cooling,*

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INTRODUCTION

Chemotherapy induced Alopecia (CIA) is one of the most complained and cause the highest distress in breast cancer patients with chemotherapy (1,2). According to Charalambous (2019), the incidence of CIA is 70% and usually occurred in women diagnosed with breast cancer. The implications of the emergence of CIA in patients have an impact on decreasing body image, decreasing patient self-esteem, and increasing psychological distress which result in decreased quality of life in breast cancer patients (2,4). In fact, many breast cancer patients refuse to continue chemotherapy due to several side effects caused by anticancer drugs, one example is alopecia (5).

CIA occurs because chemotherapy induce mitotic activity quickly and interfere with normal anagen growth in hair follicles, resulting in hair loss (6). CIA usually is just temporary and the hair begin to grow again in 3-4 weeks after the patients completed their chemotherapy (3). The severity of the patient's hair loss depend on the type of anticancer drug, dosage, drug combination and the sensitivity of the patient itself (7). Based on several studies, it is found that chemotherapy with doxorubicin, paclitaxel, docetaxel, cyclophosphamide, and/or epirubicin regimens has a very high effect of alopecia (6,8,9).

Cryotherapy or Scalp-cooling has been done for a long time to support cancer patients because it is very cheap and easy to do on patients (10). *Scalp Cooling* reducing the temperature of the patient's scalp with the aim of reducing the exposure and metabolism of cytotoxic agents to hair follicles (3,11,12). According to several studies that have been done, mechanism of *Scalp Cooling* that can reduce the incidence of alopecia by low temperature resulting in vasoconstriction, and decreased metabolic activity thus limiting the concentration of chemotherapy agents to cells so that it can decrease the effects of cytostatic agents (4,11,12).

There are several techniques for administering *Scalp Cooling* starting with frozen caps that are

replaced every 30 minutes, and *Scalp Cooling* systems (Paxman, and Dignicap) that provide a cold sensation to the patient's head covering. (12). Many studies said *Scalp Cooling* is effective to reduce the occurrence of alopecia, but this positive effect was not occurred in all patients. Many studies used less valid evaluation indicators such as the use of wigs, and subjective assessment of hair loss in patients agents (13). There are even several studies that indicate a risk of metastatic cancer to the head caused by the use of *Scalp Cooling* (10). Study that discussed scalp cooling in cancer patients to prevent alopecia is still limited. Previous literature review conducted by Ross (15) regarding to the effectiveness of scalp cooling on the prevention of alopecia. This study will review the factors that can determine the success rate of giving scalp cooling to breast cancer patients, health professionals to pay attention to these factors so that the results obtained are as expected.

METHODS

This literature study was conducted to summarize and investigate the effect of *Cryotherapy* on preventing *Chemotherapy induced Alopecia* in breast cancer patients and its determinant factors of successful *Cryotherapy*. Literature search used 4 online databases Ebscohost, Scopus, Science direct, Proquest. The keywords used are *Cryotherapy*, *Chemotherapy Induced Alopecia*, *Breast Cancer*, *Scalp Cooling*. The process of literature analysis using CASP which includes the suitability of the title with the writing theme, the research design, using English, population were breast cancer patients undergoing chemotherapy, interventions were *Scalp Cooling*, and outcome was *Chemotherapy induced Alopecia* (CIA).

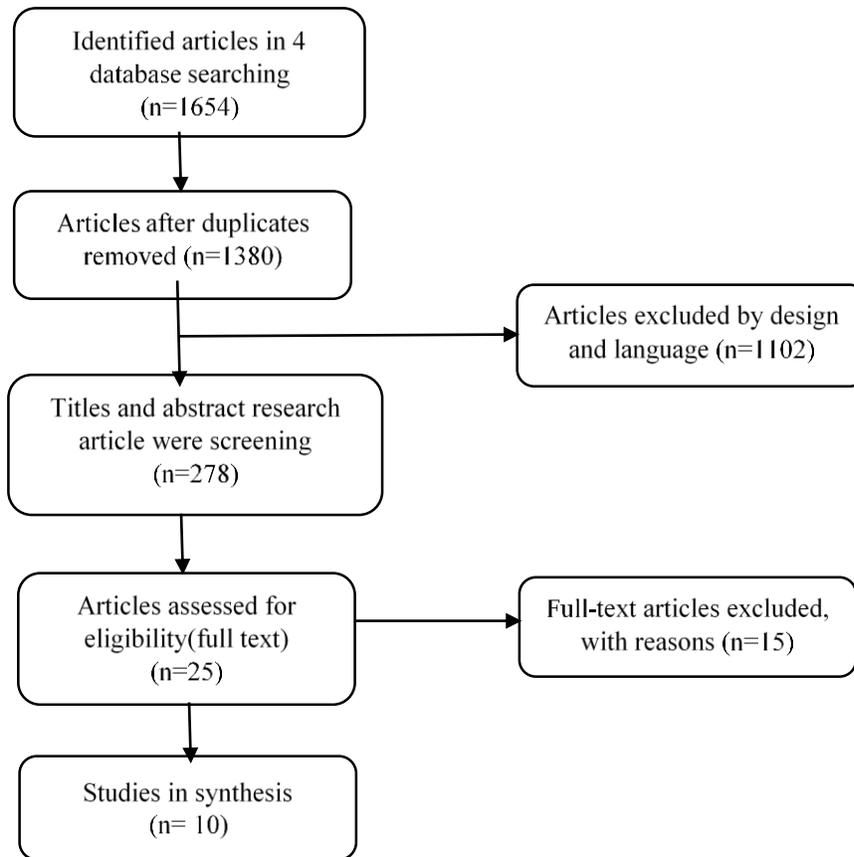
RESULTS

This study used 10 articles which relevant to *Cryotherapy*, Chemotherapy Induced Alopecia,

DISCUSSION

Figure 1. Flow chart-PRISMA recommendations

Searching was performed in four database (Scopus, Ebscohost, Science direct, and Pubmed) with a total 1654 articles which were screened including duplicates removed, language, design, title and abstract become 25 articles. 25 articles were reviewed using CASP (PICO) so that 10 articles were obtained.



Breast Cancer, and *Scalp Cooling*. The research design of 10 articles used consisted of 5 articles with the Randomized Control Trial design, 4 articles with Prospective Observational Study and 1 articles with Control Trial. From 10 journals that have been analyzed, all showed positive results and gave a significant effect of *Cryotherapy (Scalp Cooling)* on decreasing the severity of CIA in breast cancer patients. Total respondents in those journals were 1201 breast cancer patients. A summary of the literature used can be seen in table 1.

Cryotherapy (Scalp Cooling)

Cryotherapy is one of the methods used to reduce the incidence of CIA. There are 10 journals in this study that get positive results with the use of *Cryotherapy (Scalp Cooling)* which can significantly affect the incidence of CIA. There are several ways in giving *Cryotherapy* to patients, starting from the use of different devices such as Paxman, Dignicap®

Author, year	Sample and design	Participant	Device	Duration	Tools and Evaluation	Intervention Result	Control result	Adverse effect
J. Bajpai et., al. (2020)	Randomised controlled trial, two arm study	51 patients breast cancer on neoadjuvant treatment and without metastase	Paxman <i>Scalp Cooling System</i>	Scalp cooling was given 30 minutes before each cycle (precooling 30 minutes) until 90 minutes after chemotherapy.	<ul style="list-style-type: none"> - Common Terminology Criteria For Adverse Events Version 4.0 (CTCAE v4.0) - Evaluation (6 and 12 weeks) 	<ul style="list-style-type: none"> - Hair Preservation (56.3%) - (6 weeks) The HR (89%) (p = 0.0003) - (12 weeks), HR (100%) in SC 	<ul style="list-style-type: none"> - Hair preservation (0%) - (6 weeks) HR 12% in control group - (12 weeks) HR (59%) in control group 	headache and feeling coldness (98 episodes / (30%))
Julie Nangia, MD. et., al, (2018)	Multicenter randomized clinical trial	182 patients with early breast cancer stage (I-II),	Paxman <i>Scalp Cooling System</i>	before each cycle (precooling 30 minutes) until 90 minutes after chemotherapy,	<ul style="list-style-type: none"> - Common Terminology Criteria For Adverse Events Version 4.0 (CTCAE v4.0) - EORTC QLQ-C30 - HADS - BIS - Evaluation (12 eeks) 	<ul style="list-style-type: none"> - Hair preservation (48/95) (50.5%) (interim analysis) - (oncologist-graded hair preservation) (53 of 95) (55.8%) - Wigs or head wraps were used (63%) 	<ul style="list-style-type: none"> - Hair preservation (0/47) (0%) (interim analysis) - (oncologist-graded hair preservation) (0/47) (0%) - Wigs or head wraps were used (100%) 	54 adverse events Reported (headache, chills, nausea, paresthesia, pain, skin disorder and ulceration)

Author, year	Sample and design	Participant	Device	Duration	Tools and Evaluation	Intervention Result	Control result	Adverse effect
Katharina Smetanay, et., al. (2018)	Randomised controlled trial, two arm study	79 patients with breast cancer on neoadjuvant treatment	DigniCap® Scalp Cooling System	(precooling 30 minutes) with a scalp temperature maintained at 3-5°C, And until 60-120 minutes afterward.	<ul style="list-style-type: none"> - Hair pull test - Trichograms (microscopic examination) - Evaluation (3, 6 and 12 months) 	<ul style="list-style-type: none"> - Hair preservation (39.3%) ($p < 0.001$) - (Hair pull test and trichogram) (Cycle 2) 38.9% of these still Negative - (3 months) - Trichograms had recovered to a normal distribution. 	<ul style="list-style-type: none"> - Hair preservation (0%) - (Hair pull test and trichogram) (Cycle 2) all patient has a positive result - (3 months) - Trichograms had recovered to a normal distribution 	The most distressing adverse event was chills (n=24/63,1%) and headache (n=7/18,4%)
Manon M. C. Komen, et., al. (2016)	Prospective multi centre randomized study	134 breast cancer patients with docetaxel treatment 75-100 mg/m ² interval 3 weeks <i>fluorouracil, epirubicin, cyclophosphamide</i> treatment weeks	Paxman one person cooling machine (PSC-1)	(precooling 30 minutes) with temperature setting at -10°C, and until 90 or 150 minutes after chemotherapy	<ul style="list-style-type: none"> - WHO score for alopecia grades - VAS (Visual Analogue Scale) - Evaluation (6 and 12 weeks) 	<ul style="list-style-type: none"> - (90 min) proportion of patients who wore a wig (n = 16/48 (33%)) - WHO score for alopecia grade 2-3 (moderate) (n = 25/51 (49%)) 	<ul style="list-style-type: none"> - (150 min) proportion of patients who wore a wig or head cover (n = 21/46 (45%)). - WHO score for alopecia grade 2-3 (moderate) n = 17/51 (33%); p = 0,02). 	Headaches during 327 cooling as mild, moderate or severe 66 sessions.

Author, year	Sample and design	Participant	Device	Duration	Tools and Evaluation	Intervention Result	Control result	Adverse effect
Takayuki Kinoshita, et., al. (2019)	multicenter, controlled trial	48 patient with breast cancer on chemotherapy	Paxman scalp cooling was given 30 minutes	In each cycle (precooling 30 minutes) and until 90 minutes after chemotherapy in each cycle	- Common Terminology Criteria For Adverse Events Version 4.0 (CTCAE v4.0) - Evaluation (the end chemotherapy and 12 weeks after chemotherapy)	- Prevention of hair loss (26,7%) (8/30) (P = 0.011) - (12 weeks) - Hair volume recovery (25%) (5/20)	- Prevention of hair loss 0.0% (0/13) - (12 weeks) - Hair volume recovery was 8.3% (1/12) in the control group	284 adverse events :jaw pain (24/32), headache (23/32), discomfort (Chill) (68,8%), nausea (43,8%), forehead pain (40,6% and dizziness (40,6%)
Emilia Gianotti, et., al. (2019)	Multicenter interventional study, prospective observational study,	220 breast cancer patients without metastase	Paxman Scalp cooling	30 minutes prior to each cycle with temperature - 4°C for maintained scalp temperature in 18°C, and for 60 minutes after chemotherapy	- Common terminology criteria for adverse events version 4.0 - Evaluation (12 months) and follow up (16-34 months)	- (CTCAE v 4.0) Success rate of Scalp cooling (hair loss grade 0-1) was 68% or 136 patients. - 64 patients (32%) get hair loss Grade 2 - Follow-up for 24 months there was no scalp metastasis and 9 patients had breast cancer recurrence	-	migraine (n = 8), coldness (n = 4), dizziness (n = 2), and vomiting (n = 2)..

Author, year	Sample and design	Participant	Device	Duration	Tools and Evaluation	Intervention Result	Control result	Adverse effect
Ines Vasconcelos, et., al. (2018)	prospective observational single-centre study,	131 patients with breast cancer stage I-III	Paxman Scalp cooling	30 minutes before each cycle (precooling 30 minutes), and until 90 minutes after chemotherapy	- Ludwig scale for alopecia - Evaluation at each of cycle until end of chemotherapy	- The success rate was 93 patients or 73% (<50% hair loss and nor requiring a wig). - Original participants (28%) has experienced hair loss of >50% and requiring the use of wig - Success rate of Taxane-monotherapy (88%), - Success rate of anthracycline/taxane based therapy (76%)	-	headaches, nausea and discomfort
Elisabetta Munzone et. Al., 2018	a prospective clinical trial	139 Early stages breast cancer patients on adjuvant chemotherapy	Dignicap system	30 min before chemotherapy, the temperature setting between 3 °C and 5 °C. and until 90 min to 120 minutes afterward	- Dean's scale for alopecia - Evaluation (3 and 6 weeks after completed Chemotherapy)	- Hair loss prevention (56/131) (43%) - 48 patients had a hair loss grater than 50% after completing chemotherapy - Success rate in hair preservation (56 patients or 54%)	-	headaches, discomfort and coldness (n = 26) (19%); skin rash (n = 3), skin pain (n = 3) and dizziness and/or vertigo(n = 4)

Author, year	Sample and design	Participant	Device	Duration	Tools and Evaluation	Intervention Result	Control result	Adverse effect
Tommaso Giarratano 2019	A prospective study,	135 patients with early breast cancer (all patients completed the Neo-adjuvant/adjuvant Chemotherapy)	Dignicap scalp cooling system	(precooling 30 minutes) with temperature maintained at 3-5°C, and until 90-120 minutes afterward	- Dean scale - Evaluation (3 weeks after first chemotherapy until 3 weeks after the last chemotherapy)	- Success rate in alopecia prevention (77%) (104/135) at 3 weeks from the start of CT	-	Headache (60%), chills (90%), heavy head (70%) and scalp pain (56%)

differences in the duration of *Scalp Cooling* after chemotherapy is done, start from 20 minutes until 120 minutes (10 articles). Every periods of time showed a significant effect on the improvement of the patient's alopecia condition. One study conducted by Komen, et., al (2016) by comparing the duration of post-chemotherapy *Cryotherapy (Scalp Cooling)* after 20 minutes and 45 minutes found no significant difference between the groups given for 20 minutes and those given 45 minutes. Meanwhile, the research conducted by Manon C, et., al in 2018, there was a significant difference. The WHO score for grade 2-3 alopecia was more significant in the 90 minute group (n = 25/51 (49%) compared with 150 minutes post chemotherapy *Cryotherapy* (n = 17/51 (33%)). This was also shown by Bajpaj studies that patients given *Scalp Cooling* showed significant differences in hair preservation than the control group (p = 0.00004)

Mechanism of *Cryotherapy (Scalp Cooling)*

There are several theories that explain how the mechanism of *Cryotherapy* can prevent the occurrence of CIA. In this study, based on 10 journals that have been analyzed, showed that giving *Cryotherapy* has a significant positive effect on reducing CIA. The mechanism of *Cryotherapy* in reducing CIA is that it causes vasoconstriction in the scalp area of the patient, resulting the decrease of blood flow to hair follicle areas and decreasing the uptake of chemotherapy agents (12). Additionally according to Bajpaj and Smetanay et al., (2019). *Scalp Cooling* can reduce a patient's hair follicle metabolism rate so that it can help prevent hair loss.

Factors Affecting the Successfull of *Scalp Cooling*

The effectiveness of *Cryotherapy* is influenced by many factors include the type of chemotherapy which given to patient, the dose obtained by the patient, the device used in *Scalp Cooling* (Paxman, DigniCap®), the duration of *Scalp Cooling*, and the temperature setting used in *Scalp Cooling*. According to research conducted by Emilia Gianotti

(2019)(17)(17)(16)(16)(15) with setting the temperature at *Scalp Cooling* -18°C can prevent the incidence of alopecia with a success rate between 50-70%. The evaluation process in assessing the success rate of *Scalp Cooling* is still very diverse in each study including hair preservation, hair loss, hair regrowth, the need for the use of headgear for patients.

Adverse effect of *Cryotherapy*

There were some patients who complains mild side effects from *Cryotherapy (Scalp Cooling)* and there also patients who couldn't tolerate the side effects, so they were dropped out from the study. Based on the analysis that has been done, the most complained side effects from the patients during the study were headaches, felt uncomfortable due to cold, nausea and even appeared blister in patient's forehead area after given *Cryotherapy*. Therefore, it is important to continuously monitoring the patient's condition in order to anticipate the emergence of side effects from *Cryotherapy*.

DECLARATION OF INTEREST

The author declared no conflict interest

LIMITATION OF STUDY

Only studies published in English language from four databases (Ebscohost, Scopus, Science direct, Proquest) were accessed for this study. There are several types of research designs in the literature used and small number of RCT's identified (5 articles). Critical appraisal only used CASP for assess all studies.

CONCLUSSION

Cryotherapy significantly reduce the severity of CIA by inhibit the process of mitosis and vasoconstriction. There are several factors that must be considered when giving *Cryotherapy*, such as type of chemotherapy, dosages, devices, duration of administration, and temperature.

The number of adverse effects caused in scalp cooling is one of the determining factors for patients to continue scalp cooling or not. The nurses who are health professional have the longest contact with patients, must monitor the patient's condition (side effect of scalp cooling) regularly, so if problem arise, health professional can be anticipated properly and do not interfere process of giving scalp cooling. For further research, it is important to considered some factors that can affect the successfull of *Cryotherapy* and the patient response.

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