

ISSN: 2158-284X

Volume 8, Number 7, July 2017



International Journal of Clinical Medicine



ISSN : 2158-284X



9 772158 284007 07

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ISSN: 2158-284X (Print) ISSN: 2158-2882 (Online)

<http://www.scirp.org/journal/ijcm>

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Journal Information

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Clinical Research on Efficacy of Cassia Twig Tuckahoe Capsule and Mifepristone Combined with Laparoscopic Surgery for the Treatment of Endometriosis

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How to cite this paper: Banu, H., Rajoria, P., Li, H., Ju, W.H. and Liu, H. (2017) Clinical Research on Efficacy of Cassia Twig Tuckahoe Capsule and Mifepristone Combined with Laparoscopic Surgery for the Treatment of Endometriosis. *International Journal of Clinical Medicine*, 8, 463-471.

<https://doi.org/10.4236/ijcm.2017.87043>

Received: June 25, 2017

Accepted: July 23, 2017

Published: July 26, 2017

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Abstract

Objective: To compare the clinical efficacy of Cassia Twig Tuckahoe capsule (Chinese Medicine) and Mifepristone combined with laparoscopic surgery for the treatment of endometriosis. **Designs:** Prospective cohort study. **Setting:** Gynecology and Obstetrics Department, Jingzhou Central Hospital, affiliated to Yangtze University. **Methods:** We selected 67 patients suspected with endometriosis and divided randomly into 2 groups on patient choice. **Outcome Measures:** Treatment efficacy, side effects, recurrence rate and pregnancy rate. **Results:** Comparing the effect of treatment between the two groups, the success rate was almost same ($P > 0.5$). However, the disappearance of pain was faster in Cassia twig Tuckahoe group ($P < 0.05$). One patient in mifepristone group had recurrent endometriosis after 8 months from initial treatment. Comparing the side effects between the two groups, Cassia twig Tuckahoe capsule group has fewer side effects in comparison to mifepristone group. The pregnancy rate was 72% in Cassia twig Tuckahoe group while 40% in mifepristone group. **Conclusion:** After analysis of the result, Cassia twig Tuckahoe capsule combined with Laparoscopy is superior to the Mifepristone combined with Laparoscopy. Cassia twig Tuckahoe capsule is a very propitious medicine for treating endometriosis for long term benefits.

Keywords

Cassia Twig Tuckahoe Capsule, Chocolate Cyst, Endometriosis, Laparoscopy, Mifepristone

1. Introduction

Endometriosis means the presence of endometrial glandular tissue outside the uterine cavity. These cells invade and proliferate locally or distantly forming functional endometriotic implants. These implants behave like normal endometrium *i.e.* they proliferate and bleed in conjunction with menstruation cycles. The exact etiology is unknown since Von Rokitonsky has proposed the term “EM” 1860 [1]. However, there are many theories explained in books and literature such as Implantation theory, Coelomic theory, Metastatic Theory and Induction Theory [2]. The most accepted theory is Implantation Theory [3]. Still research is going on to find most potent etiology such as Genetic [4], Immune Factors [5] [6], Inflammatory factors [7] [8] [9], Environment toxins [10] [11] because it occurs in certain women but not all women. Endometriosis is also considered as an estrogen dependent disorder which affects one in every ten of reproductive age.

The most common presenting symptoms are cyclical pain (dysmenorrhea), irregular bleeding, menorrhagia, dyspareunia, chronic pain (more than 6 months of non cyclic pain) and infertility [12].

The definitive diagnosis of endometriosis can only be achieved visually via laparoscopy. Although non-invasive methods for detecting endometriosis are currently under developed, such as the CA125 Antigen [13], ultrasound scanning [14], and endometrial nerve density [15], there are various methods of treatment for Endometriosis, Medical and Surgical (Open or Laparoscopy). Endometriosis is considered as an estrogen dependent disorder, therefore current medical therapies are centered upon lowering circulating estrogen levels. In western medicine, Hormone Replacement Therapy (HRT) is commonly used and it involves Oral Contraceptive Pills (OCPS), Progestogenic, Gestrinone, Danazole, GnRH agonist, but long term administration of these medicines remains challenging due to serious adverse side effects such as heavy bleeding, perimenopausal symptoms, masculinization and liver dysfunction. Instead of these side effects, data from Cleveland Clinic showed that the endometriosis recurrence rate was 20 - 40 percent within 5 years following conservative surgery, unless the patient reached menopause or hysterectomy [16]. Due to relatively poor efficacy of hormonal therapy, several other therapies for endometriosis are currently being used such as Mifepristone (a selective progesterone receptor modulator) [17], Dienogest (a progestin) [18]. The Chinese medicine has been also widely utilized since the 19th Century, and its utilization in China as well as in Western countries is increasing nowadays [19] [20]. But, still the best and effective treatment for endometriosis remains challenging. Keeping this in mind we planned to find the efficacy of Cassia twig Tuckahoe capsule (Chinese medicine) and Mifepristone combined with laparoscopy for the treatment of endometriosis.

2. Methods

From January 2014-March 2014, 67 patients suspected with endometriosis were

admitted to Gynecology and Obstetrics department of Jingzhou Central hospital for the treatment. The research was approved by the ethics committee of the Gynecology and Obstetrics department.

The inclusion criteria were:

- a) Patients presenting with typical symptoms indicating endometriosis.
- b) Ultrasound suspecting Endometriosis such as Presence of Chocolate cyst and Adhesions.
- c) Laboratory reports suspecting endometriosis such as raised CA125 and CRP positive.

The exclusion criteria:

- a) Laparoscopy diagnosis revealing other pathology than Endometriosis.

Therefore 8 patients out of 67 were excluded and the remaining 61 patients were divided into two groups according to their choice for Mifepristone (33 patients) and Cassia twig Tuckahoe (26 patients) and latter one patient dint come for follow up from the study group so she was also excluded. Finally 25 patients from the study group were given Cassia twig Tuckahoe capsule and 33 patients from the control group were given Mifepristone after Conservative laparoscopic management.

Treatment: The initial treatment for the patients in both groups was the same Conservative Laparoscopic management. Latter according to respective groups, the study group received Cassia twig Tuckahoe capsule 3 Capsule three times a day for 6 months and Control group received 10 mg 1 tablet once a day for 6 months.

Follow up: The patients in both groups were followed up on regular basis for a period of 1 year. The initial follow up was after 2 weeks from the day of discharge. Latter on this sedule was adjusted to once every 2 month for 6 month and then every 3 month for remaining 6 month. On every follow up following items were assessed: side effects, recurrence, menstruation cycle and pregnancy with the help of serum CA125 Antigen, Ultrasound, Clinical symptoms, Pelvic Examination, Liver function test and renal function test.

Statistics: The difference in categorical data between the two groups was compared using the two-sided X^2 test. SPSS 12.0 Software was used and the Significant value ($P < 0.05$) was considered statically significant.

3. Results

Demographic

The average age of all enrolled patient was 30 (range: 20 - 42). Out of these patients, 2 patients had previous history of endometriosis. The most common symptom with which patients presented was irregular bleeding with pelvic pain (Dysmenorrhea). The Ultrasound revealed that the average size of the cyst was 5 cm. On the day of hospitalization, 34 Patient presented with history of irregular bleeding and Dysmenorrhea, 14 patients presented with pelvic pain (Dysme-

norrhoea) only and 9 patients had regular cycle with dyspareunia. The severities of symptoms were mild in 9 patients, moderate in 14 patients and severe in 39 patients. The average duration of the symptoms among these patients was 3 months. There was no significant difference between the both group patients in any of above Demographic or clinical characteristic (**Table 1**).

The efficacy, Side effects, Recurrence and pregnancy rate during 1 year follow up

The overall success rate of the treatment between the two groups was almost same ($P > 0.05$). The Serum CA125 antigen regression was not significant in our study ($P > 0.05$). The average time was for Serum CA125 antigen regression was almost same. The disappearance of pain was significantly faster in the Cassia Twig Tuckahoe capsule group ($P < 0.05$) in comparison to mifepristone group. The menstruation cycle normalized in more patients in Cassia twig Tuckahoe capsule group. While in mifepristone group 9 patients complaint of menorrhagia and 5 patients developed Ammenoea during the treatment but latter after completion of mifepristone course, the cycle was regular but painful (**Table 2**).

Table 1. Comparison of the demography and clinical characteristic between two groups.

Items	Study groups (n = 25)	Control group (n = 33)	P value
Age (years)			
<30	16 (64%)	21 (63.6%)	0.992
30 - 40	5 (20%)	7 (21.2%)	
>40	4 (16%)	5 (15.2%)	
Previous H/O Endometriosis			
NO previous history	24 (96%)	32 (97%)	0.841
Previous history	1 (4%)	1 (3%)	
CA125 Antigen Level at the presentation units/ml			
20 - 50	15 (60%)	15 (45.5%)	0.543
51 - 80	7 (28%)	13 (39.4%)	
>80	3 (12%)	5 (15.2%)	
Diameter of endometriosis cyst on ultrasound			
<2 cm	2 (8%)	3 (9.1%)	0.899
2 - 5 cm	14 (56%)	20 (60.6%)	
>5	9 (36%)	10 (30.3%)	
Symptoms			
Pelvic Pain + Irregular Cycle	17 (68%)	17 (51.5%)	0.316
Pelvic pain only	4 (16%)	10 (30.3)	
Irregular Cycle only	1 (4%)	0 (0%)	
Regular cycle	3 (12%)	6 (18.2%)	
Severity of symptoms			
Mild	5 (20%)	4 (12.1%)	0.278
Moderate	6 (24%)	4 (12.1%)	
Severe	14 (56%)	25 (75%)	

Table 2. Comparison of effect, side-effect, recurrence, and pregnancy outcome during 1 year follow-up.

Items	Study groups (n = 25)	Control group (n = 33)	P value
Success	25 (100%)	32 (97%)	0.380
Unsuccess	0 (0%)	1 (3%)	
Duration of CA125 to normal level			
<1 week	15 (60%)	15 (45.5%)	0.543
1 week-2 weeks	7 (28%)	13 (39.4%)	
>2 weeks	3 (12%)	5 (15.2%)	
Disappearance of pain			
<1 months	23 (92%)	18 (54.5%)	0.008
2 - 5 months	2 (8%)	13 (39.4%)	
6 - 12 months	0 (0%)	2 (6.1%)	
Menstruation cycle			
Normal	24 (96%)	19 (57.6%)	0.004
Menorrhagia	1 (4%)	9 (27.3%)	
Amenorrhoea	0 (0%)	5 (15.2%)	
Symptoms Related to medicine			
No any symptoms	19 (76%)	13 (39.4%)	0.033
Nausea	5 (20%)	12 (36.4%)	
Vomiting	1 (4%)	5 (15.2%)	
Headache	0 (0%)	3 (9.1%)	
Renal Function Test			
Normal	23 (92%)	32 (97%)	0.397
Dearranged	2 (8%)	1 (3%)	
Liver Function Test			
Normal	24 (96%)	25 (75.8%)	0.035
Dearranged	1 (4%)	8 (24.2%)	
Ultrasound Reports			
Normal	24 (96%)	32 (97%)	0.354
Small Collection in POD	1 (4%)	0 (0)	
Recurrence	0 (0%)	1 (3%)	
Pregnancy rate			
Natural Conception	9 (36%)	5 (15.2%)	0.039
In vitro fertilization	9 (36%)	8 (24.2%)	
Not Conceived	7 (28%)	20 (60.6%)	

During the follow up periods, many patients complaint Nausea and vomiting which were more prominent in mifepristone group, as a short term side effect. One patient in Cassia twig Tuckahoe capsule group and 8 patients in control group reported abnormal Liver Function Test, which shows significant between the two groups ($P < 0.05$). While the renal abnormalities were not significant in our study (**Table 2**).

An ultrasound evaluation was performed for all patients. 2 weeks after the initial treatment. Among them small collection in Pouch of Douglas were found in 1 patient in the Cassia twig Tuckahoe capsule group for which one course of Metronidazole was given and it disappear at the next follow up ultrasound evaluation. 1 patient from the mifepristone group has recurrence after 8 months of initial treatment for which the patient had to go again for laparoscopic surgery for the management. She was among the 5 patient in whom Serum CA125 regress after 2 weeks.

The pregnancy rate was significant in our study ($P < 0.5$). 9 patients conceived naturally and 9 patients conceive with the help of In vitro fertilization (IVF) while in mifepristone group 5 patients conceived naturally and 8 patients with the help of IVF during our study period (**Table 2**).

4. Discussions

Previously Endometriosis was considered to be an estrogen dependent that affected women approaching middle age, but now it is recognized that to disease diagnosed more frequently in younger women [21]. In our study the mean age for endometriosis was 30 years. Endometriosis is not only a heavy burden for the sufferer, but also in economic terms too. The loss of work has caused by illness (severe pain, visiting clinics for treatment) due to endometriosis is estimated to the U.K. economy 2 billion pounds a year [22].

The Diagnosis of endometriosis has still not improved and usually misdiagnosed or diagnosed latter. The Definitive diagnosis of endometriosis can only be achieved visually via Laparoscopy. Although non invasive methods for detecting endometriosis are currently under developed, such as the CA125 Antigen [13], Ultrasound scanning [14], and endometrium nerve density [15]. For this reason 8 patients were excluded from our study because they had other pathology rather than endometriosis at laparoscopic management.

There is various method of treatments, medical and surgical (Open or Laparoscopy). Due to relatively poor efficacy of hormonal therapy, several other therapies such as mifepristone [17], Dienoyst [18] are used now a day. These can be used either before surgery if mild endometriosis or can be used after surgery. Many study revealed better result when combined with surgery. Now a day's Chinese medicine is gaining more popularity in china as well as in western countries with less side effect and similar success rate in comparison to mifepristone. [19]. Similarly in our study the success rate of both medicines were almost same.

The side effects that were reported after the use of each medicine were generally in the same range as those reported by other investigators [20]. One study showed that if high dose of mifepristone is given over a prolong period promotes an unopposed oestrogen milieu leading to endometrial hyperplasia, resulting in massive bleeding [23]. In our study Menorrhagia was the most prominent in mifepristone group in spite of using low dose mifepristone. The Mifepristone

have many other side effects too such as nausea, vomiting, headache, liver and renal impairment while the Cassia twig Tuckahoe does not have any such side effects other than nausea and vomiting which were also less in comparison to mifepristone. Two patients had some renal function derangement in cassia twig Tuckahoe capsule group but it may be due to diabetes because both of these patients had diabetes.

The cassia twig Tuckahoe is a very propitious medicine for dysmenorrhea as well chronic pelvic pain. One clinical trial showed that cassia twig Tuckahoe could relieve dysmenorrhea as effectively as mifepristone, with total effective rate 90% and 73% in cassia twig Tuckahoe capsule group and mifepristone groups respectively after 3 month of treatment with a study group of 120 patients [24]. Similar result was also observed with clinical trial of 42 patients treated with cassia twig Tuckahoe capsule for 6 months.

The comparison of recurrence rate in our study with those of other study is more [25]. The recurrences were more in mifepristone group. This may be due to long period of follow-up and endometrial hyperplasia leading to menorrhagia and reflux of menstruation (Implantation Theory).

In our study the overall 1 year commutative rate of pregnancy was 72% in Cassia twig Tuckahoe capsule group and 40% in mifepristone group. Cassia twig Tuckahoe is a very good for infertility treatment due to endometriosis. It normalize the menstruation cycle as well sex hormone and increase sexual desire which can increase the conception but further study on this topic is required. Other study also reported a higher pregnancy rate in Cassia twig Tuckahoe capsule group, 5 out of 10 endometriosis patients with infertility were pregnant in comparison to mifepristone [26]. Mifepristone decreases estrogen, progesterone, luteinizing hormone and makes endometrial incapable for implantation which is against pregnancy [27] [28] [29].

5. Conclusion

After analysis of result, Cassia twig Tuckahoe capsule combined with Laparoscopy is superior to the Mifepristone combined with Laparoscopy with regards to fewer side effects, better natural conception rate, less relapse and less menstruation disorders for the management of endometriosis. However, the success rate of both types of treatment is almost same. It should be popularized for the treatment of endometriosis for the long term patient's benefits.

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Analysis of Sudden Cardiac Arrest during Marathon Races in Japan

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How to cite this paper: Shirakawa, T., Tanaka, H., Kinoshi, T., Tanaka, S. and Takyu, H. (2017) Analysis of Sudden Cardiac Arrest during Marathon Races in Japan. *International Journal of Clinical Medicine*, 8, 472-480.

<https://doi.org/10.4236/ijcm.2017.87044>

Received: June 25, 2017

Accepted: July 25, 2017

Published: July 28, 2017

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Abstract

Objective: Increased number of runners in Japan has been one reason for increasing the risk of cardiac arrest during marathon races. The purpose of the study was to examine 1) the incidence of cardiac arrest during marathon races held in the past in Japan, 2) the characteristics of runners with cardiac arrest, 3) the effectiveness of public access defibrillation (PAD) use for cardiac arrest cases. **Methods:** We examined the incidence of the cardiac arrest during marathon races in Japan from the medical records of marathon races that Kokushikan University provided in the past five years. Also, we analyzed cardiac arrests occurred in Japan in the past 15 years between 1999 and 2013. **Results:** The incidence rate of cardiac arrest was 2.18 per 100,000 participants. As shown in **Table 1**, the incidence rates were 2.00 per 100,000 participants in full marathon and 2.50 per 100,000 participants in half-marathon. A total of 63 cardiac arrests occurred in the past 15 years, and the number of incidents has been increasing every year. Among 63 cardiac arrest cases, the mean age was 45.3 ± 14.9 years old and 93.7% (59/63 cases) were in males. Eighty-three percentage of cardiac arrest cases applied AED (20/24 cases) were the shockable rhythm. In terms of the survival rate, there was a statistically significant difference between the cases where both bystander CPR and PAD were delivered and the cases where the only bystander CPR took place without PAD (95.0% vs. 47.1%; $p < 0.05$). In Japan, the case of the PAD use during marathon races has been increasing since the use of AED was permitted for public citizens in 2004. **Conclusions:** Performing PAD on the scene during marathon races could be expected to be higher in the survival rate. Creating a medical support system is needed to handle sudden cardiac arrest rapidly in order to perform early bystander CPR and PAD.

Keywords

Sudden Cardiac Arrest, Marathon Race, PAD, Bystander CPR

1. Introduction

In recent years, marathon has been not only categorized within competitive sports as top athletes run in the Olympic games, but also spread as a popularized sport. In fact, the number of runners and marathon races has been gradually increasing every year.

It is thought that increasing the number of competitive marathon runners has a certain efficacy of promoting good health, but, at the same time, the risk of those runners' sudden cardiac arrest occurrence during marathon races has also been increasing. Kuroyanagi *et al.* reported 534 cases of sudden death in sports occurred in Tokyo prefecture between 1948 and 1999 and the cardiac arrests occurred the most in running as there were 118 cases during running [1]. In fact, seven cardiac arrest cases were reported from the past 10 Tokyo Marathon races, which have been held between 2007 and 2016 [2].

The medical support system for those marathon races has been changed. As the use of AED was permitted for public citizens in 2004, races implemented AED has been increasing in Japan. In fact, some cases of AED use for cardiac arrest during marathon have been reported. However, the implementation of AED for marathon races leading to the improvement on the survival rate of cardiac arrest in marathon is not clearly known. In terms of the incidence rate of cardiac arrest during marathon races, Kim *et al.* and Hart reported 0.54 per 100,000 participants suffered from cardiac arrests during marathon races in the U.S. between 2000 and 2010 [3] [4]. Especially in the U.S., 1.01 per 100,000 participants suffered in full marathon, and 0.27 per 100,000 participants suffered in half-marathon [3] [4]. According to the study by Pedoe *et al.*, the incidence rate of the cardiac arrest on London Marathon was 2.17 per 100,000 participants in the past 26 years between 1981 and 2006 [5]. Moreover, regarding the characteristics of runners with cardiac arrests, 86.4% (51/59 cases) were occurred in males [3] [4], as well as other research indicated that males had more tendency to become cardiac arrests [6]. However, there is no study that has been reported about its characteristics in Japan.

The purpose of this study was to see the incidence of the cardiac arrest occurrence, characteristics of runners with cardiac arrest and the effectiveness of defibrillation by AED. We analyzed the cardiac arrest cases during marathon races held in Japan.

2. Method

2.1. Study Design

A nationwide retrospective study of cardiac arrests during marathon races.

2.2. The Method of How to Calculate the Incidence of the Cardiac Arrests during Marathon Races

There were a total of 18 full marathons and 39 half-marathons that Kokushikan University provided the medical supports between April 2008 and March 2013. We investigated the total number of runners applying from either official announcement on the race website or interviewing to the marathon race committee. We also investigated the numbers of cardiac arrests from the medical support records and calculated the incidence rate of cardiac arrest during those marathon races.

2.3. The Method of How to Collect Data of Cardiac Arrests Occurred during Marathon Races and Analysis Items

We extracted cardiac arrests occurring where marathon races was held in Japan during 15 years between 1999 and 2013, from the Asahi Shimbun online article database “Kikuzo II Visual for Libraries[®]”, the internet, and journal articles. For each cardiac arrest case, we asked each race committee for the detailed examination.

On questionnaire, we asked the detail of runners who went to cardiac arrest, such as sex, age, the type of race, the location of cardiac arrest occurrence, the time of race started, the time of when cardiac arrest occurred, bystander CPR, AED application, defibrillation by AED, and outcome.

2.4. Statistical Analysis

We used Microsoft[®] Excel[®] for data analysis. Chi-Square test was used to compare the survival rate, and level of significance was set at 0.05.

2.5. Consent and Ethical Considerations of the Study

We gave a clear explanation to subjects regarding the purpose of the study for each question. We made sure that subjects will not take disadvantages when they refused to participate in the study. We followed the Act of the Protection of Personal Information and we carefully handled personal information as all individual information will not go to the public. The study was approved by the Institutional Review Board at Kokushikan University.

3. Result

3.1. The Incidence of the Cardiac Arrests during Marathon Races (Table 1)

Kokushikan University provided the medical coverage for a total of 57 races (18 full marathons and 39 half-marathons) between April 2008 and March 2013. The total number of runners were 459,479 (299,691 people in full marathon and 159,788 in half-marathon) and 10 cardiac arrests occurred (6 cases in full marathon and 4 cases in half-marathon). The mean age of 10 cases was 45.8 ± 17.8 years old, and all 10 cases occurred in male.

The incidence of cardiac arrest was 2.18 per 100,000 participants. As shown in

Table 1. Cardiac arrest incidence and type of marathon.

	No of Attendant	No. of Cardiac Arrest	Incidence (per 100,000)
Overall	459,479	10	2.18
Full Marathon	299,691	6	2
Half Marathon	159,788	4	2.5

Table 1, the incidence was 2.00 per 100,000 participants in full marathon, and 2.50 per 100,000 participants in half-marathon.

3.2. The Number of Cardiac Arrests during Marathon Races in Japan

We extracted 63 cardiac arrest cases (26 cases in full marathon and 37 cases in half-marathon) from the past 15 years between 1999 and 2013. We divided into the three sections for every-five-year. There were 18 cases between 1999 and 2003, 22 cases between 2004 and 2008, and 23 cases between 2009 and 2013. The number of cardiac arrests gradually increased.

3.3. Background Data of Cardiac Arrest Cases during Marathon Races in Japan (Table 2)

Males were accounted for 93.7% (59/63 cases) of cardiac arrests during marathon races. Cardiac arrest occurred within the wide range as the mean age was 45.3 ± 14.9 years old (Min: 20-year-old; Max: 70-year-old).

In order to analyze the location of cardiac arrest occurrence, we assumed 0% of the race at the start line and 100% at the finish line. For the full marathon, the majority of cardiac arrests occurred at the 50% - 74% point and the 75% - 99% point. For the half-marathon, 75% - 99% point and the finish line had the majority of cases.

In terms of the speed of runners who went cardiac arrest, the average speed was 10.8 ± 3.2 km/h (Min: 6 km/h; Max: 21.6 km/h). The majority of cardiac arrests occurred for runners who run under 9.9 km/h in full marathon, and runners who run with 10.0 - 14.9 km/h in half-marathon.

3.4. The Effectiveness of AED and Survival Rate on Cardiac Arrests during Marathon Races

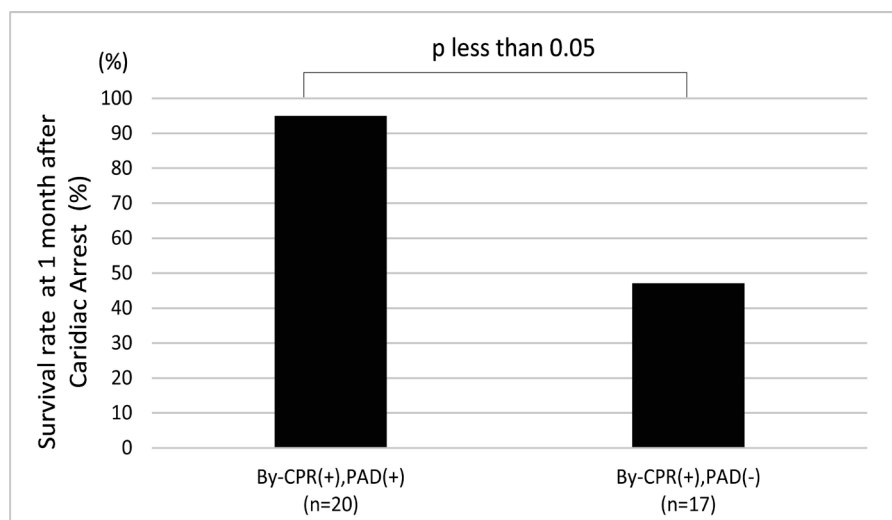
The survival rate of cardiac arrests during marathon races was 54.0% (34/63 cases). However, the every-five-year survival rate was increased as follows: 22.2% (4/18 cases) between 1999 and 2003, 63.6% (14/22 cases) between 2004 and 2008, and 69.9% (16/23 cases) between 2009 and 2013. We highlighted the increased survival rate after 2004, because AED was implemented for marathon races.

3.5. The Survival Rate of the Use of PAD

Within the 47 cases performed bystander CPR on the scene, we analyzed the survival rate after one-month on 37 cases of them, which were known to be if the

Table 2. Patients background.

	Overall (n = 63), (%)	Full Marathon (n = 26), (%)	Half Marathon (n = 37), (%)
Facial Year			
1999 - 2003	18, (28.6)	8, (30.8)	10, (27.0)
2004 - 2008	22, (34.9)	8, (30.8)	14, (37.8)
2009 - 2013	23, (36.5)	10, (38.5)	13, (35.1)
Gender			
Male	59, (93.7)	26, (100.0)	33, (89.2)
Female	4, (6.3)	0, (0.0)	4, (10.8)
Age			
20 - 29 (yr.)	14, (22.2)	3, (21.4)	11, (29.7)
30 - 39 (yr.)	10, (15.9)	3, (21.4)	7, (18.9)
40 - 49 (yr.)	11, (17.5)	6, (23.1)	5, (13.5)
50 - 59 (yr.)	16, (25.4)	9, (34.6)	7, (18.9)
60 - 69 (yr.)	10, (15.9)	4, (15.4)	6, (16.2)
70 - 79 (yr.)	2, (3.2)	1, (3.8)	1, (2.7)
Place occurrence cardiac arrest			
start - 24% point	(n = 56) 4, (7.1)	(n = 23) 2, (8.7)	(n = 33) 2, (6.1)
25 - 49% point	4, (7.1)	1, (4.3)	3, (9.1)
50 - 74% point	11, (19.6)	10, (43.5)	1, (3.0)
75 - 99% point	18, (32.1)	9, (39.1)	9, (27.3)
Finish line	19, (33.9)	1, (4.3)	18, (54.5)
Speed of cardiac arrest runner			
~ 9.9 km/h	(n = 38) 18, (47.4)	(n = 16) 11, (68.8)	(n = 22) 7, (31.8)
10.0 - 14.9 km/h	16, (42.1)	5, (31.3)	11, (50.0)
15.0 km/h ~	4, (10.5)	0, (0.0)	4, (18.2)



By- CPR: Bystander CPR
 PAD: Public access defibrillation

Figure 1. Survival rate between PAD and non PAD patients.

defibrillation by AED on the scene was used. Twenty cases were given defibrillation and 17 cases were not. The survival rate after one-month was 95.0% (19/20 cases) when the defibrillation was administered, and 47.1% (8/17 cases) when the defibrillation was not administered. A significant difference was found between the presence or absence of defibrillation by AED ($p < 0.05$) (Figure 1).

The details of 20 cases of the presence of defibrillation were as follows: zero cases between 1999 and 2003, eight cases between 2004 and 2008, and 12 cases between 2009 and 2013. The case with the use of defibrillation was significantly increased after 2004.

3.6. Precision of Defibrillation with Runners with Cardiac Arrest

Twenty-seven cases were identified with the application of AED on the scene. Of which, 24 cases were known to be if the defibrillation by AED on the scene was used, and the percentage of administering defibrillation was 83.3% (20/24 cases). From the analysis, we identified that 83% of runners with cardiac arrest during marathons races would have shockable rhythm, ventricular fibrillation or pulseless ventricular tachycardia.

4. Discussion

From this study, the incidence of cardiac arrest during marathon races in Japan was 2.18 per 100,000 participants. This is quite similar to the study from England (2.17 per 100,000 participants), and we have four times greater than the study from the U.S. (0.54 per 100,000 participants) [3] [4] [5]. In terms of the incidence of cardiac arrests during marathon races, cardiac arrests occurred quite often in Japan compared to the other countries. We thought the incidence rate of cardiac arrest was influenced by increasing the number of competitive marathon runners and a wide range of runner population, especially in elderly. From the previous study, 40 cardiac arrests occurred in full marathons and 19 cardiac arrests occurred in half-marathons among 10.9 million participants [3] [4]. Although the incident of cardiac arrest per 100,000 was higher in full marathons from the study by Kim *et al.* and Hart [3] [4], our study indicated half-marathons was higher in danger as we found 2.0 per 100,000 in full marathons and 2.5 in half-marathons. This is because there are a larger number of half-marathons held in Japan than full marathons. Since half-marathons has a shorter distance, the higher percentage of runner who is not well-trained.

Regarding the characteristics, cardiac arrest was occurred not only with elderly, but also with a wide range of age group between 20's and 70's. Males were accounted for 93.7% (59/63 cases) from our study, and also Kim *et al.* reported 86.4% and Hart reported 86 % of cardiac arrest cases occurred in males [3] [4]. As well as Waite *et al.* also found males are more in danger to become cardiac arrest [6], we conclude that males were one of risk factors of cardiac arrest during marathon race from the result of our study and the previous study.

In terms of location, we found that the majority of cardiac arrest occurred in

the second half of the race. Different higher risk points existed between full marathon and half-marathon. For full marathon, 50% - 74% point were the most, followed by 75% - 99% point. For half-marathon, the finish line was the most, followed by 75% - 99% point. Cardiac arrests at the finish line were reported in the U.S. [7]. From our result, we need to consider the higher risk of location and put medical coverage for these spots.

The mean speed of runners who went to cardiac arrest was 10.8 ± 3.2 km/h (Min: 6 km/h; Max: 21.6 km/h). Most of cardiac arrests occurred when runners run under 9.9 km/h for full marathon, and 10.0 - 14.9 km/h for half-marathon. From this result, running with 10.0 km/h at the beginning of the second half of the race was the highest risk. We need to take this into consideration for the future medical coverage during a marathon.

Compared to 29% of survival rate among the 59 cardiac arrests from the study by Kim *et al.* and Hart [3] [4], we had 54.0% of survival rate among 63 cases. The survival rate in Japan was higher than those in the U.S. The survival rate was improved every year as shown in the every-five-year division. Compared to 22.2% (4/18 cases) between 1999 and 2003, we have had better result since AED was implemented for marathon races in 2004. The rate rapidly improved to 63.3% (14/22 cases) between 2004 and 2008, and 69.6% (16/23 cases) between 2009 and 2013. The crucial factor was the implementation of AED for marathon races, so the number of defibrillation administration by AED was increased under the situation of cardiac arrest during marathon races. In fact, in comparison to zero cases between 1999 and 2003, the case of defibrillation administration by AED was increased to eight cases between 2004 and 2008, and 12 cases between 2009 and 2013.

In cardiac arrests where bystander CPR was performed on the scene, the survival rate after one-month was 95.0% (19/20 cases) of cardiac arrests treated with defibrillation, and 47.1% (8/17 cases) for cardiac arrest treated without defibrillation. There was two times more difference, and a statistically significant difference was found ($p < 0.05$). Also, defibrillation was given in the 83.3% of the cases where AED was applied. From this result, a cardiogenic cause was accounted for the majority of cardiac arrest during marathon races. Kuroyanagi *et al.* reported 81% of sudden death in sports in Japan was caused by a heart-related disease [1]. In other countries, researchers reported that heart-related disease is the majority of cause of cardiac arrest during marathon races [7] [8] [9].

We did not examine the risk of cardiac arrest and the reduction factors in our study, there are several studies indicating the importance of screening prior to the race and the efficiency of taking prophylactic Aspirin [10] [11]. Cardiac arrest could be occurred in marathon even with adequate prevention, so creating the medical support systems is needed to handle sudden cardiac arrest rapidly.

5. Conclusion

We analyzed the incidence rate of cardiac arrest during marathon races in Japan,

and the number of cardiac arrests occurred in Japan during the past 15 years. The incidence of cardiac arrest during marathon races in Japan was 2.18 per 100,000 participants. Runners would go into cardiac arrest run at a speed of 10 km/h and the most cases occurred in the second half of a race.

Also, 83% of cardiac arrests were shown as shockable rhythm and could be able to deliver defibrillation by AED. We found 95% of the survival rate after one-month when both bystander CPR on the scene and defibrillation by AED were administered. Since 2004, the use of AED by citizens was permitted and the survival rate was rapidly improved during marathon races. We think the reason behind is increased public access defibrillation (PAD) along with the implementation of AED at marathon races.

We expect higher survival rate due to conducting PAD on the scene. We also need to take risk factors into consideration for medical coverage on marathon races, especially the location and a time period. Thus, we need to create a medical support system that would be able to perform bystander CPR earlier and PAD for runners.

Acknowledgements

We express our extraordinary respect for all marathon staff in Japan for their efforts.

Contribution

TS carried out the all studies, statistical analysis, and drafted the manuscript. HT participated in the design of the study, and performed the statistical analysis. HT performed the statistical analysis and drawing figures and tables. ST conceived of the study, and participated in its design and coordination. TK advised and assisted in the planning of this paper and ST helped to revise the manuscript. All authors read and approved the final manuscript.

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