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Table of Contents

Volume 8 Number 1

January 2017

Patient Safety Attitudes, Skills, Knowledge and Barriers Related to Reporting Medical Errors by Nursing Students

H. Safarpour, M. Tofighi, L. Malekian, J. Bazayr, S. Varasteh, R. Anvary.....1

Evaluation of Antioxidant, Lipid Peroxidation and Toxic Effects after Pomegranate Intake in Healthy Human Volunteers

P. Faizal, B. Satheesan, B. Vinod, K. T. Augusti.....12

Aortic Dissection after Percutaneous Coronary Intervention for Acute Coronary Syndrome: An Outcomes-Based Study from the Nationwide Inpatient Sample Database

C. S. M. Lau, G. J. McRoy, K. Mahendraraj, K. P. Kulkarni, R. S. Chamberlain.....21

Thiol-Disulfide Homeostasis in Patients with Panic Disorder

B. Kulaksizoglu, S. Kulaksizoglu.....34

Beliefs and Clinical Practice for Complex Regional Pain Syndrome (CRPS) Managed by Physiotherapists on the South Island of New Zealand

T. Pons, E. A. Shipton, R. T. Mulder.....42

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Patient Safety Attitudes, Skills, Knowledge and Barriers Related to Reporting Medical Errors by Nursing Students

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Abstract

Introduction: Health care system structure is prone to human error. Medical errors are one of the major challenges that health systems in all countries are grappling with to minimize and reduce the damage caused by them. The aim of this study was to assess the Patient Safety Attitudes, Skills, Knowledge and Barriers Related to Reporting Medical Errors by Nursing Students in Ilam, Iran. **Methods:** A cross-sectional mixed method was conducted to this study. Sampling was conducted by census of all students entering nursing criteria in Ilam in 2016. A number of 140 students participated in this study. The tool used in this study was created by Schnall *et al.* that measures knowledge, attitudes and skills related to medical errors reporting. Data were analyzed with t test, regression and correlation coefficients and descriptive statistical methods. **Results:** The results showed that nursing students had a positive attitude with respect to the reporting of medical errors ($p = 0.01$). They also have the low knowledge to medical errors and reporting them. There were significant differences in all groups and subgroups of knowledge, attitude, and skills (except creating of safety culture subgroup) between the two group's students. Moreover, the main reason for not reporting was the lack of knowledge and fear of punishment. **Conclusions:** The results of this study help those who involve in the health care system to improve patient safety and improve the process of reporting medical errors by nursing students' participation in the process of reporting error, while improving knowledge and attitudes through nursing

education with the effective educational models. As a result, there is a need to educate students on reporting systems.

Keywords

Medical Error, Reporting Error, Nursing Students, Barriers, Ilam

1. Introduction

Health care system structure is prone to human errors. Medical errors are one of the major challenges that health systems in all countries are grappling with to minimize and reduce the damage caused by them. Studies show that 3 - 17 percent of patients admitted to hospitals suffer an injury or condition that occurs as a result of medical errors or adverse event [1]. According to the Institute of Medicine in 1999, approximate 44 to 98 thousand people have lost their lives as a result of medical errors [2]. In the United States, approximate 400 thousand deaths from medical errors occur annually and medical errors are the third leading cause of death in the United States [3]. Patients are entitled to safe care by health care providers. To prevent and reduce medical errors, health care system as a whole needs to change policies and procedures. Although evidence suggests that recurrence of medical errors can be prevented by the reporting system, but medical errors continue because of the lack of reporting of medical errors. Results of a study showed that 50 to 96 percent of medical errors are not reported. In addition it was shown that 96% of medical errors are not evaluated or their recurrence in the future is not prevented [4]. Many studies were conducted on the use of medical errors reporting systems and barriers associated with these systems by nurses. Barriers identified by the nurses include: the completion of error reporting time, lack of knowledge about the occurrence of error, belief in the need to report an error, providing an error as reality or denial, embarrassment or fear of punishment for error reporting [5] [6]. Various studies have linked the lack of knowledge regarding the reporting of medical errors as common barrier. According to the Department of Health and Human Services, the hospital staff does not report 86 percent of medical errors, partially due to inadequate understanding of that what damage can happen to their patients by failing to report [7]. Medical errors reporting system should take priority in accordance with health care providers training and evaluation report. Understanding and identifying reporting errors and barriers to it can help to increase the percentage of reporting medical errors. There will be strong and effective changes in the attitudes and behavior of employees, if provided with repeated and reinforced education [8]. Nursing education programs should include medical errors reporting training to introduce them repeated in and increased use of errors reporting system. Cooper in 2012 stated that introducing errors reporting system in the early years of education could reduce barriers to reporting and improve the error reporting [9]. Health care providers can be very effective to

reduce the number of errors that occur by using error reporting system [10]. It is estimated that each year over three million preventable adverse events occur in hospitals [11]. Knowing the underlying causes of these errors is necessary to prevent a repeat occurrence of similar incidents. However, to understand the root causes of such errors, first, in most cases, the error should be repeated. The potentially harmful nature of these errors, the number of medical errors that occur in hospitals is unacceptable. Thereby reducing the incidence of medical errors must be a priority to improve patient safety [12]. The evaluation of reporting barriers in reporting systems is a fundamental step to reduce medical errors and improve patient safety. Nursing students are key beneficiaries in an effort to reduce medical errors with the ability to help to improve medical errors reporting systems. Promote clear understanding of medical errors and barriers to reporting are essential to develop effective measures to increase the use of error reporting systems. Therefore, the objective of this study is to understand the barriers to reporting medical errors by nursing students.

Hospitals and other health service providers must take action to improve the reporting of medical errors and improve quality of care through learning from mistakes. In general, the reporting of medical errors should become a culture in health care centers, and this is to boost the use of error reporting systems by reducing the fear of punishment. Many studies have examined barriers to reporting of medical errors through physician and nurses perspectives, however, few studies conducted on the barriers to reporting and perception of medical errors by nursing students. Therefore, awareness of the importance of reporting medical errors should be started during nursing education. All health care professionals, including nursing students are required to report medical errors. Balas *et al.* (2004) studied 393 nurses and showed that 30 percent of nurses have reported at least one error [13]. Nursing students may have much concern for various reasons to report a medical error; however, the attitude towards the reporting of medical errors could be affected through appropriate education and creating culture of reporting. Knowing the barriers to use medical error reporting systems by students can help the importance of nursing education in promoting the safety culture [14]. Yaghobi *et al.* (2015) results titled “The incidence of medication errors in nursing students and their views on not reporting the error among senior nursing students” using a questionnaire containing 17 statements about students' demographic characteristics and causes of not reported medication errors in the three domains of fear of the consequences of reporting, management factors and reporting factors show that among the aspects surveyed the higher score went to reporting factors, that forgetting the medication errors reporting by students accounted for most points. Given the domains of fear of the consequences of reporting medication errors by a student the fear of news dissipation in the faculty and among other students gained the higher score. Moreover, in the area of management factors higher scores went to the disproportionate instructor's reaction to the severity and importance of errors in reporting and forgetting the medication errors reporting by students. Also fear of news dissipa-

tion in the faculty and among other students, absence of a precise definition of medication errors, fear of informed the physician and blamed by them, fear of error detection and legal problems followed, and unimportance of medication errors reporting from the perspective of students were the five main causes of not reported medication errors by students in terms of single causes of not reported medication errors by nursing students [15]. Another study (2012) was conducted to examine the causes of not reporting medical errors from the perspective of nursing managers, supervisors, and head nurses in all clinical wards of a hospital. In this study the causes of not reporting medical errors has been classified in four categories. Results show fear of punishment by direct supervisor, high workload the individual exposed to charge and considering error reporting as useless were of great importance. Also created extra work for the person (to report) and loss of reputation or job were of the utmost importance from both groups perspectives. The cost of ineffective reporting from the supervisor's perspective gained the least importance, but was of the utmost importance from head nurse perspectives. Moreover, the possibility of cancelling the employment contract was of the most importance on the view of supervisors, but with the least importance on the view of head nurses [16]. Another study examines barriers to reporting by nurses and doctors to modify the this behavior, The questionnaire used in the study also showed that barriers to reporting and lack of adequate knowledge and allowed researchers to determine the most adjustable barriers. The barriers include structure and process as well as lack of knowledge [6]. According to the authors study, specifically, the use of questionnaires is the most common method to study the reporting barriers. Healthcare Research and Quality Agency proposed two different tests to evaluate the overall safety culture in 2012: Examination of patient safety culture and safety attitudes questionnaire [17]. While these tests help to determine the perceived safety of health care, none specifically assess knowledge. Many studies have reported a lack of knowledge as a barrier in medical errors reporting [18] [19]. As a result, to add knowledge assessment, as part of future studies to examine barriers to reporting medical errors by nursing students is important. Therefore, the aforementioned study should be modified to be used in this study and knowledge assessment should be added as part of this tool. One of the developed tools that added knowledge assessment as part of the evaluation is Schnall *et al.* (2008) test of patient safety knowledge, skills and attitudes [20]. According to above literature, the aim of this study was to assess the Patient Safety Attitudes, Skills, Knowledge and Barriers Related to Reporting Medical Error by Nursing Students in Ilam, Iran.

2. Methods

A cross-sectional mixed method (quantitative and qualitative) was conducted to this study. Sampling was conducted by census of all students entering nursing criteria in Ilam in 2016. A number of 140 students participated in this study, 18 of whom were Master of Science in nursing student (MSN) and 122 were Ba-

chelor of Science in nursing student (BSN). Inclusion criteria included: students who passed at least one course of clinical practice in a hospital environment. The exclusion criteria were dissatisfied students, freshmen without hospital and clinical backgrounds. The tool used in this study was Patient Safety attitudes, skills and knowledge scale (PS-ASK) that created by Schnall *et al.* (2008). This tool has been created for use in nursing programs and therefore was suitable to examine the study variables. This tool items were based on five-scale Likert including three content groups including knowledge, skills and attitude. Attitude scale consists of 9 items and was divided into three subgroups of error detection, time investment and creating a culture of safety. Literature has determined that attitude, as lack of knowledge is a common barrier to medical errors reporting [21] [22] [23]. Skills scale consists of 13 items and was divided to the subgroups of error analysis, decision support technology, and threats to patient safety. Knowledge scale consists of 4 items. However, this tool was not able to measure some barriers to reporting medical errors which could affect the nursing students such as understanding the need to report the error, fear of punishment or fear of creating a problem for the another; therefore to get more information an open-ended questions was added to the questionnaires study other barriers [19]. The open-ended question was “Is there anything that may prevent you from completing an error report after a near miss or adverse event occurs?” First, the questionnaire was translated into Farsi by two people fluent in English. Then to match it with the English questionnaire was translated into English by two linguists. Content validity test was used to check for validity. The tool was handed to 10 college experts. After examining the content validity, the index of 0.87 was reported. To pilot test, 30 questionnaires were distributed among 30 samples and after 10 days the test-retest was conducted. Cronbach’s alpha coefficient was measured after data was collected using SPSS 21 software. Alpha coefficient of 0.81 was calculated in this study. All parts of the questionnaire data and qualitative open-ended question were analyzed separately. After data collection, data analysis was performed using the SPSS v.19 software. Descriptive statistics were calculated. Normality of data distribution was confirmed by Kolmogorov-Smirnov test. Then, data was analyzed with t test, regression and correlation coefficients and descriptive statistical methods. Significance as well as $P \leq 0/05$ was determined.

3. Results

The number of 140 students participated in this study, 12.9% ($n = 18$) were MSN student and 87.1% ($n = 122$) were BSN students. **Table 1** shows the demographic characteristics of nursing student in this study.

The mean and standard deviation were compared based on two groups of BSN and MSN students with inclusion criteria. **Table 2** shows the overall scores of attitude, skills and knowledge and associated subcategories. The results showed that students’ attitudes about medical errors were higher among MSN student. Also, there was a significant difference between skill category especially

Table 1. Demographic characteristics of nursing students.

Characteristics		Frequency (Percent)
Sex	Female	82 (58.6%)
	Male	58 (41.4%)
Marital Status	Single	113 (80.7%)
	Married	27 (19.3%)
Level of Education	BSN student	122 (87.1%)
	MSN Student	18 (12.9%)

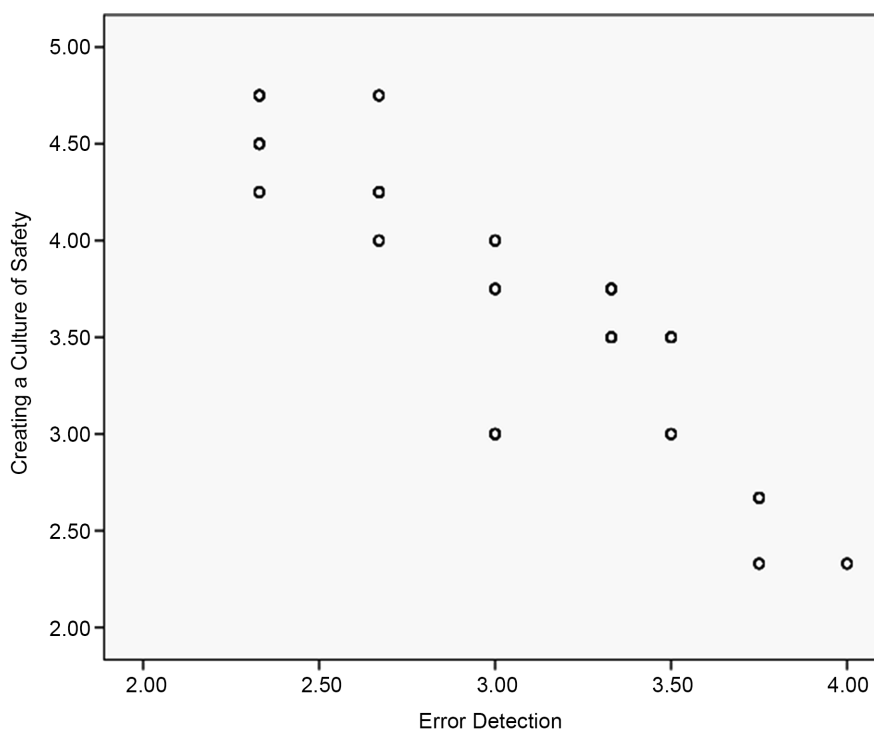
Table 2. Overall Scores of Attitude, Skills and Knowledge and Associated Subcategories.

	N	Mean	SD
Attitude	140	3.86	0.25
Error Detection	140	4.07	0.46
Time Investment	140	4.26	0.70
Creating a Culture of Safety	140	3.26	0.66
Skills	140	2.75	0.65
Error Analysis	140	1.9	0.74
Decision Support Technology	140	3.71	0.75
Threats to Patient Safety	140	3.30	0.76
Knowledge	140	2.96	0.91

in the threats to patient safety subcategory in both groups ($p = 0.0001$) and MSN students showed higher confidence and were able to provide and improve patient safety. **Table 3** outlines the differences between the two student groups in each category and subcategory. There was no significant difference between the creating a culture of safety in both groups ($p = 0.43$). Also there is statistically significant difference in the subcategory of error detection in the skills category and MSN students' attitudes were more in error detection ($p = 0.0001$). In addition, results showed that there was a significant difference between the two groups in terms of knowledge and the knowledge of MSN students was more ($p = 0.007$). There was a negative statistically significant relationship between the two subcategories of creating a culture of safety and error detection ($p = 0.034$, $r = -0.7$) (**Figure 1**). Also There was a negative coefficient correlation between the creating a culture of safety and knowledge and students whose attitudes were more toward creating a culture of safety had less knowledge about the safety of patients ($p = 0.003$, $r = -0.6$). These results show the important effects of creating a culture of safety. The highest positive response went to the error detection and the highest negative response was to creating a culture of safety. This shows that students' attitude was more toward creating a culture of safety and less toward errors detection. In addition, results showed that most students understand

Table 3. BSN and MSN nursing students Scores of Attitude, Skills and Knowledge and Associated subcategories.

	Mean (SD) MSN Students	Mean (SD) BSN Students	p Value
Attitude	3.91 (0.31)	3.81 (0.23)	0.01
Error Detection	3.94 (0.46)	4.27 (0.41)	0.0001
Time Investment	4.39 (0.50)	4.09 (0.90)	0.003
Creating a Culture of Safety	3.23 (0.65)	3.31 (0.72)	0.43
Skills	2.95 (0.69)	2.50 (0.53)	0.0001
Error Analysis	2.10 (0.80)	1.65 (0.60)	0.0001
Decision Support Technology	3.88 (0.78)	3.50 (0.67)	0.001
Threats to Patient Safety	3.53 (0.69)	3.01 (0.77)	0.0001
Knowledge	3.17 (0.90)	2.70 (0.89)	0.007

**Figure 1.** Correlation between creating of culture and error detection.

the importance of reporting medical errors. Some students also had negative attitudes and this could indicate that enhanced the experience and knowledge related to patient safety and reporting medical errors can lead to cynical perspective when involved in medical errors reporting. In addition, the higher score of knowledge of students on patient safety was in correlation with lower scores in the attitude towards patient safety. In other words, most of the students who had more knowledge about patient safety had fewer attitudes towards creating a culture of safety. There was a significant positive relationship between knowledge

and error analysis subgroup, and students with more knowledge were more skillful in error analysis ($p = 0.002$). For aim to reporting error asked an open-ended question to nursing students. 103 of student (74%) answered to open-ended question: “is there anything that may prevent you from completing an error report after a near miss or adverse event occurs?” 87 samples stated the followings: fear of punishment, reaction and pressure from staff, lack of knowledge and confidences about the occurrence of error, being out of their business, neglecting their responsibility to report an error, a lack of knowledge about how to report and notoriety among the other students and Staff. The greatest reason for not reporting was lack of knowledge and fear of punishment. Overall findings showed that students are afraid of reporting errors and lack enough knowledge.

4. Discussion

Patient safety must be the first priority of Health care provider. Theoretical grounds should be combined with educational experiences following the development of knowledge, skills and attitudes for effective patient safety. Evaluation of nursing students’ attitude towards the reporting of medical errors is important because attitudes can affect behavior. There was no enough study about medical errors in nursing students for better comparison. Our study results indicated that the positive attitude of students toward medical errors reporting has a valuable effect on improving patient safety and in contrast creating the culture of safety showed less effect. The answer to open-ended question results showed that barriers such as fear of punishment and pressure by other staff after error reporting reflect the culture of the students in the academic environment. Reporting culture should be a norm on health care environment. Learning how the system and attitude cause errors is the first step in the development process to prevent similar errors in the future. Create a punitive culture associated with medical errors has little effect on reducing errors [24]. Safety culture, although ideal, may not be applicable in all areas. The results showed that there is a condition of uncertainty about the safety culture in health care in nursing students. Statements, such as fear of punishment and errors detection, may be followed with problems reflects the punitive culture of nursing environment. Skills gained lower scores than other aspects, and students were at lower levels of competency in the risk analysis subgroup. Nurse’s knowledge on understanding of medical errors and reporting them was low. Overall findings showed that students are afraid of reporting errors and lack enough knowledge, thus requiring reporting systems trainings.

5. Conclusion

Improving patient safety should be the goal of all health care professionals which should start as a strong base of experience and education of professional health care specialists. The current study emphasis is on medical errors reporting and patient safety that should be included in nursing training programs. The study

showed nurses lack of knowledge and attitude in relation to patient safety. Nursing programs may be somewhat improved the situation, but students will not acquire adequate skills and knowledge as long as nursing education is not based on a model and purposeful. Although there are processes in reports of medical errors, nursing students are not involved in this process and, therefore, students do not have enough skills to analyze the error. The study shows the need to create a culture of reporting to assist medical errors reporting in Training nurses. Creating and developing a culture of reporting could reduce students' fear of errors reporting resulting in improving the reporting process and ultimately may cause a professional positive attitude towards the reporting of medical errors. Based on the results of open-ended questions, to clarify reporting was one of the problems and a number of participants indicated that there is the lack of transparency in the reporting of medical errors in the academic environment. Transparency can help students understand the importance of errors reporting. Therefore, students must participate in the process of error analysis and be informed of the changes that occur as a result of reporting the same errors in the future. The results of this study help those who involve in the health care system to improve patient safety and improve the process of reporting medical errors by nursing students' participation in the process of reporting errors, while improving knowledge and attitudes through nursing education with the effective educational models.

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Evaluation of Antioxidant, Lipid Peroxidation and Toxic Effects after Pomegranate Intake in Healthy Human Volunteers

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Abstract

Studies have extensively demonstrated the activation of enzymic and non-enzymic antioxidants as well as decrease of lipid peroxidation status after pomegranate intake without any observable toxicity in animal models. Comparing to animal model studies, human trials are less done on these aspects. Cellular damage caused by reactive oxygen species appears to be a major contributor in ageing and other degenerative diseases such as cancer, cardiovascular diseases, cataracts, compromised immune system, rheumatoid arthritis and brain dysfunction. Several literatures show that pomegranate has been used as a folk medicine from ancient times itself. As per the reviews, pomegranate fruit possesses antioxidant, anti-inflammatory, antiatherogenic and antitoxic effects. The primary objective of this study was to evaluate the circulatory levels of selected antioxidant and lipid peroxidation marker in healthy human volunteers before and after pomegranate intake for a period of 0 - 90 days. As the secondary objective of the study, we also assessed the toxic effects of pomegranate supplementation by determining Hepatobiliary and Renal function tests. The final result showed that majority of the study population showed a significant increase in enzymic and non-enzymic antioxidants and a decrease in oxidative stress after pomegranate intake without any observable toxicity in liver function and renal function. The significant healthy variations were more after the intake of pomegranate for a period of 90 days than that of 45 days.

Keywords

Oxidative stress, Reactive Oxygen Species, Phytochemicals, Pomegranate

1. Introduction

Epidemiologic studies have shown significant inverse relationship between the incidence of various diseases and dietary intake of fruits and vegetables [1]. Free radicals have been implicated in the pathogenesis of many diseases. There is a growing evidence that excessive production of free radicals can cause or exacerbate many human diseases [2] [3]. Pomegranate has been used in folk medicine from ancient times owing to its potential health benefits [4]. The various phytochemicals present in this fruit are potent antioxidants and anti-inflammatory agents, thereby counteracting oxidative damage and inflammation which is responsible for the pathogenesis of various diseases [5] [6] [7]. The antioxidant property of pomegranate juice was shown to be three times higher than that of red wine and green tea based on the evaluation of the free radical scavenging and iron reducing capability of the juices [5]. It possesses significantly higher levels of antioxidants in comparison with the commonly consumed fruit juices [8] [9]. The major antioxidant polyphenols present in the pomegranate fruit include the ellagitannins and anthocyanins [10]. Punicalagin is the major ellagitannin present in the fruit [11]. Clinical studies with relation to this fruit are comparably lesser with that of animal trials. As there are only limited, but promising human data, the present study aimed to further strengthen support for the unique antioxidant and antiperoxidative properties of this healthy fruit. The primary objective of this study was to evaluate the circulatory levels of selected antioxidant and lipid peroxidation marker in healthy human volunteers before and after pomegranate intake for a period of 0 - 90 days. As the secondary objective of the study, we also assessed the toxic effects of pomegranate supplementation by determining hepatobiliary and renal function tests.

2. Materials and Methods

The work has been carried out at the Dept. of Medical Biochemistry, School of Health Sciences, Kannur University. Ethical committee clearance has been obtained for the conduct of this study. An informed consent was collected from each participant prior to the study. A clinical proforma was given to each participant to collect data such as height, weight, sex, dietary pattern and previous history of illness. A total number of 40 healthy human volunteers in each group (age group of 18 - 65 yrs) as adjudged from their clinical features were selected for the study. They were divided into three groups as Group Ia—Healthy human volunteers before pomegranate intake, Group Ib—Healthy Human volunteers after 45 days of pomegranate intake and Group Ic—healthy human volunteers after 90 days of Pomegranate intake. Pomegranate fresh fruit was purchased from the local market of thalassery, kannur dist, kerala from where which the people belong to the study normally purchase the fruits from. Dosage of the fruit was fixed in such a manner that prior to this study another trial was conducted in which varying doses of pomegranate were given to healthy human volunteers, the varying doses were 50 g/day, 100 g/day, 150 g/day and 200 g/day out of these

groups a significant percentage difference in antioxidant activity and antiperoxidative activity were shown in groups which consumed at least 100 g/day and more, so in this study 200 g/day was given, which showed maximal activity among the varying dosages used for the study in the previous trials. Participants suffering from any diseases/disorders that may interfere with the study were excluded. 5 mL of blood sample was taken for the analysis. Study was designed for a period of 90 days. Blood samples were collected before the intake, 45 days after the intake and 90 days after the intake of fresh pomegranate fruit at a dosage of 200 g/day. Serum/Plasma was separated and estimated using the standard methods. The major enzymic antioxidants analysed were Catalase (Maehly and Chance) [11], Superoxide dismutase (Marklund & Marklund) [12], Glutathione peroxidase (Paglia & Valentine) [13], Glutathione reductase (Goldberg and Spooner) [14] and glutathione-S-transferase (Beutler) [15]; the major non-enzymic antioxidants determined were glutathione (DTNB) [16], Vitamin C (2,6-Dichlorophenol Indophenol) [17] & Vitamin E (Baker & Frank) [17]. The lipid peroxidation marker estimated was Malondialdehyde (Beuge *et al.*) [18]. For determining the toxic effects of the fruit, if any, Hepatobiliary function was assessed by determining the levels of Total Bilirubin (Jendrassik & Grof) [19], Total Protein (Biuret) [20], Albumin (BCG) [20], Globulin (Friedwald's formulae), AST (UV, Kinetic) [21], ALT (UV, Kinetic) [21] and ALP (pNPP-AMP) [21]; Renal function was assessed by estimating the levels of Urea (GLDH-Urease) [22], Uric acid (Uricase/oxidase) [22] and Creatinine (Jaffes) [22] according to the methods mentioned in the parenthesis by authors names. The data was analysed by using sigmaplot 13 version. $P < 0.05$ that was treated has statistically significant.

3. Results

Inter group comparison of serum SOD levels (Table 1 & Table 2) shows a statistically significant increase between Group Ia and Ib ($P < 0.003$) with a highly significant increase between Group Ia and Ic & Group Ib and Ic ($P < 0.001$). The percentage increase was more in between Initial and final levels followed by Mid and final level & Initial and Mid level in the order $12.8 > 8 > 4.4$.

Inter group comparison of serum CAT levels (Table 1 & Table 2) shows a statistically significant increase between Group Ia and Ib ($P < 0.049$) with a highly significant increase between Group Ia and Ic & Group Ib and Ic ($P < 0.001$). The percentage increase was more in between Initial and final levels followed by Mid and final level & Initial and Mid level in the order $62.4 > 37.9 > 17.7$.

Inter group comparison of serum Glutathione peroxidase levels (Table 1 & Table 3) shows a statistically significant increase between Ib and Ic ($P < 0.005$) with a highly significant increase between Group Ia and Ic ($P < 0.001$). The percentage increase was more in between Initial and final levels followed by Mid and final level & Initial and Mid level in the order $23.9 > 14.3 > 8.3$. Even though there is no statistically significant change between Group Ia and Ib there is a dif-

ference in the mean percentage increase of value.

Inter group comparison of serum Glutathione reductase levels (**Table 1** & **Table 3**) shows a statistically significant increase between Ib and Ic ($P = 0.005$) with a highly significant increase between Group Ia and Ic ($P < 0.001$). The percentage increase was more in between Initial and final levels followed by Mid and final level & Initial and Mid level in the order $24.4 > 15.2 > 8.0$. Eventhough there is no statistically significant change between Group Ia and Ib there is a difference in the mean percentage increase of value.

Inter group comparison of serum Glutathione S transferase levels (**Table 1** & **Table 3**) shows a statistically significant increase between Ib and Ic ($P = 0.049$) with more significant increase between Group Ia and Ic ($P = 0.004$). The percentage increase was more in between Initial and final levels followed by Mid and final level & Initial and Mid level in the order $11.3 > 7.4 > 3.6$. Eventhough there is no statistically significant change between Group Ia and Ib there is a difference in the mean percentage increase of value.

Inter group comparison of serum Glutathione levels (**Table 4** & **Table 5**) shows a statistically significant increase between Ib and Ic ($P = 0.01$) with a highly significant increase between Group Ia and Ic ($P < 0.001$). The percentage increase was more in between Initial and final levels followed by Mid and final level & Initial and Mid level in the order $21.0 > 12.5 > 7.5$. Even though there is no statistically significant change between Group Ia and Ib there is a difference in the mean percentage increase of value.

Inter group comparison of serum Vitamin C levels (**Table 4** & **Table 5**) shows a statistically significant increase between Ib and Ic ($P = 0.001$) with a highly significant increase between Group Ia and Ic ($P < 0.001$). The percentage increase was more in between Initial and final levels followed by Mid and final level & Initial and Mid level in the order $29.0 > 18.7 > 8.7$. Even though there is no statistically significant change between Group Ia and Ib there is a difference in the mean percentage increase of value

Inter group comparison of serum Vitamin E levels (**Table 4** & **Table 5**) shows a statistically significant increase between Group Ia and Ib ($P = 0.001$), with a highly significant increase between Ia and Ic & Ib and Ic ($P < 0.001$). The percentage increase was more in between Initial and final levels followed by Mid and final level & Initial and Mid level in the order $25.7 > 17.8 > 8.5$.

Inter group comparison of serum MDA levels (**Table 4** & **Table 6**) shows a statistically highly significant decrease in all groups studied ($P < 0.001$). The mean percentage decrease was more in between Initial and final levels followed by Mid and final level & Initial and Mid level in the order $-17.4 > -12.4 > -5.7$.

Inter group comparison of Liver function parameters viz; serum Total Bilirubin, Total Protein, Albumin and Globulin, AST, ALT, ALP (**Table 7**, **Table 8**, **Table 9** & **Table 10**) and renal function parameters viz; Blood urea, serum uric acid and creatinine (**Table 11** & **Table 12**) were statistically insignificant in all groups studied, showing that supplementation of pomegranate does not have any toxic effects for the organs liver and kidney.

Table 1. Mean \pm SD levels of enzymic antioxidants in Group I, before and after supplementation of pomegranate fruits.

Mean \pm SD	Parameter				
	SOD (U/mL)	CAT (IU/L)	GPX (U/L)	GR (IU/L)	GST (IU/L)
	R.R = 2.80 - 3.95	R.R = 10 - 50	R.R = 95 - 206	R.R = 30 to 80	R.R = 4.30 - 6.40
0 day (a)	3.13 \pm 0.12	18.6 \pm 5.1	148.93 \pm 22.86	49.62 \pm 8.48	4.97 \pm 0.48
Group I 45 day (b)	3.27 \pm 0.16	21.9 \pm 6.3	161.34 \pm 26.69	53.58 \pm 10.54	5.15 \pm 0.57
90 day (c)	3.53 \pm 0.20	30.2 \pm 6.0	184.49 \pm 28.48	61.75 \pm 8.68	5.53 \pm 0.69

Table 2. Inter Group comparison, t value, p value and mean difference % of SOD and CAT.

Groups	SOD			CAT		
	t value	p value	MD %	t value	p value	MD %
IaVsIb	3.031	0.003	4.4	2.004	0.049	17.7
IaVsIc	8.660	<0.001	12.8	7.044	<0.001	62.4
IbVsIc	5.629	<0.001	8	5.040	<0.001	37.9

Table 3. Inter Group comparison, t value, p value and mean difference % of GPX, GR and GST.

Groups	GPX			GR			GST		
	t value	p value	MD %	t value	p value	MD %	t value	p value	MD %
IaVsIb	1.680	0.097*	8.3	1.509	0.136*	8	1.085	0.281*	3.6
IaVsIc	4.814	<0.001	23.9	4.621	<0.001	24.4	3.377	0.004	11.3
IbVsIc	3.134	0.005	14.3	3.113	0.005	15.2	2.291	0.049	7.4

Table 4. Mean \pm SD levels of non-enzymic antioxidants & MDA in Group I before and after supplementation of pomegranate fruits.

Mean \pm SD	Parameter			
	GSH (mg/dL)	Vit. C (mg/dL)	Vit. E (mg/L)	MDA (nmol/mL)
	R.R = 15 - 55	R.R = 0.6 - 1.4	R.R = 6 - 19	R.R = 8 - 20
0 day (a)	23.51 \pm 3.50	0.69 \pm 0.12	11.20 \pm 0.90	8.45 \pm 0.35
Group I 45 day (b)	25.28 \pm 3.82	0.75 \pm 0.16	12.15 \pm 1.04	7.97 \pm 0.26
90 day (c)	28.45 \pm 4.20	0.89 \pm 0.13	14.32 \pm 1.10	6.98 \pm 0.20

Table 5. Inter Group comparison, t value, p value and mean difference % of Glutathione, Vit.C and Vit.E.

Groups	Glutathione			Vitamin C			Vitamin E		
	t value	p value	MD %	t value	p value	MD %	t value	p value	MD %
IaVsIb	1.625	0.108*	7.5	1.540	0.128*	8.7	3.303	0.001	8.5
IaVsIc	4.536	<0.001	21	5.134	<0.001	29	10.849	<0.001	25.7
IbVsIc	2.911	0.010	12.5	3.594	0.001	18.7	7.545	<0.001	17.8

Table 6. Inter Group comparison, p value, t value and mean difference % of MDA.

Groups	MDA		
	t value	p value	MD %
IaVsIb	6.128	<0.001	-5.7
IaVsIc	18.766	<0.001	-17.4
IbVsIc	12.638	<0.001	-12.4

Table 7. Mean \pm SD levels of Liver function parameters in Group I, before and after supplementation of Pomegranate fruits; (b) Mean \pm SD levels of Liver function parameters in Group I, before and after supplementation of pomegranate fruits.

(a)				
Mean \pm SD	Parameter			
	Bilirubin (mg/dL)	T. Protein (g/dL)	Albumin (g/dL)	Globulin (g/dL)
	R.R = 0.2 - 1.0	R.R = 6 - 8	R.R = 3.5 - 5.0	R.R = 1.8 - 3.6
0 day (a)	0.34 \pm 0.08	6.82 \pm 0.410	4.18 \pm 0.15	2.64 \pm 0.26
Group I 45 day (b)	0.36 \pm 0.10	6.88 \pm 0.56	4.22 \pm 0.11	2.66 \pm 0.45
90 day (c)	0.39 \pm 0.12	6.95 \pm 0.58	4.25 \pm 0.16	2.70 \pm 0.42

(b)			
Mean \pm SD	Parameter		
	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
	R.R = 8 - 40	R.R = 5 - 35	R.R = < 350
0 day (a)	15.8 \pm 4.98	19.82 \pm 4.62	68.5 \pm 15.35
Group I 45 day (b)	16.68 \pm 3.06	20.26 \pm 4.00	71.9 \pm 17.8
90 day (c)	18.08 \pm 5.42	21.17 \pm 3.60	78.8 \pm 22.96

Table 8. Inter group comparison, t value, p value and mean difference % of Bilirubin and Total Protein.

Groups	Bilirubin			T. Protein		
	t value	p value	MD %	t value	p value	MD %
IaVsIb	0.698	0.488*	5.8	0.406	0.686*	0.9
IaVsIc	1.745	0.235*	14.7	0.88	0.764*	1.9
IbVsIc	1.047	0.508*	8.3	0.474	0.868*	1

Table 9. Inter group comparison, t value, p value and mean difference % of Albumin and Globulin.

Groups	Albumin			Globulin		
	t value	p value	MD %	t value	p value	MD %
IaVsIb	0.998	0.540*	0.9	0.183	0.855*	0.8
IaVsIc	1.747	0.234*	1.7	0.550	0.928*	2.3
IbVsIc	0.749	0.456*	0.7	0.367	0.919*	1.5

Table 10. Inter group comparison, p value, t value and mean difference % of AST, ALT and ALP.

Groups	AST			ALT			ALP		
	t value	p value	MD %	t value	p value	MD %	t value	p value	MD %
IaVsIb	0.676	0.501*	5.6	0.380	0.705*	2.2	0.634	0.528*	4.9
IaVsIc	1.752	0.232*	14.1	1.166	0.574*	6.8	1.920	0.166*	15
IbVsIc	1.076	0.490*	8.4	0.786	0.68*	4.5	1.286	0.364*	9.6

Table 11. Mean \pm SD levels of Renal function parameters in **Group I**, before and after supplementation of pomegranate fruits.

Mean \pm SD		Parameter		
		Bl. Urea (mg/dL)	Uric acid (mg/dL)	Creatinine (mg/dL)
		R.R = 15 – 40	R.R = 3.5 - 7.0	R.R = 0.6 - 1.4
Group I	0 day (a)	24.50 \pm 4.46	4.18 \pm 0.95	0.91 \pm 0.17
	45 day (b)	23.33 \pm 3.32	4.46 \pm 0.820	0.88 \pm 0.14
	90 day (c)	25.24 \pm 3.47	4.62 \pm 0.68	0.95 \pm 0.13

Table 12. Inter Group comparison, t value, p value and mean difference % of Bl.Urea, Uric acid and Creatinine.

Groups	Bl.Urea			Uric acid			Creatinine		
	t value	p value	MD %	t value	p value	MD %	t value	p value	MD %
IaVsIb	1.093	0.479*	-4.8	1.201	0.413*	6.7	0.718	0.475*	-3.3
IaVsIc	0.691	0.492*	3	1.888	0.178*	10.5	0.958	0.566*	4.4
IbVsIc	1.785	0.218*	5.2	0.686	0.495*	3.6	1.676	0.266*	7.9

4. Discussion

Dose effects of supplementary feeding of Pomegranate in healthy human volunteers show that all enzymic and non-enzymic antioxidant levels were raised in the blood significantly for both 45 days and 90 days of feeding without any observable toxicity. When we consider the effect of feeding highly significant dose effects were observed in the group who were served pomegranate for 90 days. Pomegranate fruits used in this experiment are fully enriched with several antioxidants such as phytosterols, polyphenols, flavanoids, carotenoids and Vitamins especially E & C [9] [10]. In addition to the above, several minerals such as iron that promote synthesis of haemoglobin and selenium, that promotes glutathione peroxidase action are also there in this fruit. The finding that 90 days of feeding with pomegranate was more effective than 45 days may be due to the fact that the human body cells are more exposed to the antioxidants enriched components of the fruit. Pomegranate contains antioxidants such as anthocyanins, ellagic acid, gallic acid, punic acid, catechin, EGCG, quercetin, rutin, apigenin and other flavanoids ellagitannins and triterpenoids such as ursolic, merlinic and ariatic acids, out of which EGCG is the strongest antioxidant with

eight hydroxyl groups and this may be the reason that pomegranate activates the enzymic and nonenzymic antioxidants of the body and reduces lipid peroxidative effects.

5. Conclusion

The study has shown that consumption of 200 mg/day of Pomegranate exerts beneficial effects in human body by increasing the antioxidant defense mechanism and reducing lipid peroxidation without any observable toxicity. Pomegranate contains various nutraceuticals which are all endowed with increasing antioxidant activity and decreasing the oxidative stress. Most of the active principles contained in the fruit must have protected the cells from oxidative stress and the insignificant change in liver function and kidney function parameters indicates that there is no toxic effect for this wonder fruit and as a result it can be consumed in day-to-day life for increasing the antioxidant potential of the cells and thereby the total health status of the body can be improved to a great extent. Further clinical studies in this regard with large sample size have to be continued in order to further strengthen the role of this fruit as an immune booster.

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Aortic Dissection after Percutaneous Coronary Intervention for Acute Coronary Syndrome: An Outcomes-Based Study from the Nationwide Inpatient Sample Database

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Abstract

Introduction: Aortic dissection is a rare complication of Percutaneous Coronary Intervention (PCI) for Acute Coronary Syndrome (ACS), but is associated with mortality rates of up to 20%. This study assessed the demographic and clinical profile of a large cohort of patients undergoing PCI for ACS to assess patient and clinical risk factors that may predispose to the development of aortic dissection. **Methods:** The Nationwide Inpatient Sample (NIS) database (2001-2011) was used to abstract admission data on patients undergoing PCI for ACS. **Results:** 777,595 patients underwent PCI and 380 (0.05%) developed aortic dissection. Patients who developed aortic dissection were more often older (68 vs. 64 years), female (47.4% vs. 33.8%), insured through Medicare (56.2% vs. 50.7%), Medicaid (7.9% vs. 5.3%) or uninsured/self-pay (6.3% vs. 4.7%), $p < 0.05$. Patients with aortic dissection had a higher rate of ventricular fibrillation (6.3% vs. 1.8%), cerebrovascular accident (2.4% vs. 0.4%), longer lengths of hospitalization (9 days vs. 3 days), as well as higher mortality (13.2% vs. 1.4%), $p < 0.001$. Multivariate analysis identified female gender, Hispanic race, uninsured/self-pay, fluid and electrolyte disorders, and peripheral vascular disease (PVD) as independent risk factors for aortic dissection after PCI. **Conclusion:** Aortic dissection is a rare complication of PCI, which occurs more often in older patients with Medicare insurance status. Hispanics, females, uninsured patients and those with PVD are at the highest risk of aortic dissection. Clinicians should be more cognizant of patients at increased risk of developing PCI in order to institute earlier screening in high-risk patients.

Keywords

Aortic Dissection, Percutaneous Coronary Intervention, NIS

1. Introduction

Percutaneous Coronary Intervention (PCI) is widely recognized as an effective treatment for Acute Coronary Syndrome (ACS), and over half a million PCI procedures are performed each year in the United States (US) [1]. Despite significant advances and extensive individual experience with interventional cardiology procedures, aortic dissection remains a rare complication. Aortic dissection occurs with an estimated incidence of < 0.1% following PCI procedures, and is associated with increased in-hospital mortality (20% - 50%) as well as other severe complications [2] [3] [4] [5].

Given its rarity, current knowledge regarding which patient risk factors are associated with an increased occurrence of aortic dissection following PCI remains limited. At present, only scant data on risk factors associated with aortic dissection following PCI exist and are limited primarily to single case studies or small retrospective cohort studies, which makes it of little value in risk stratifying or predicting which patients are at risk.

This current study examines a large cohort of patients undergoing PCI for ACS from the Nationwide Inpatient Sample (NIS) database in an effort to identify demographic and clinical factors which relate to the occurrence of aortic dissection following PCI.

2. Methods

Data for the current study was extracted from the NIS database, a part of the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ) database, over an eleven-year period (2001-2011). The NIS is the largest all-payer inpatient care database in the US, containing data on more than eight million hospital stays from over 1000 hospitals. 777,595 patients underwent PCI for ACS were identified and exported to IBM SPSS® v20.2. ACS was defined as ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina. PCI as a primary procedure was identified using ICD9 code 36.06. Acute myocardial infarction (MI) was identified using ICD-9-CM code 410 and unstable angina with 411.1. Demographic and clinical information pertaining to patient age, gender, race, admission source, primary expected payer, indication for PCI, and preexisting comorbidities was extracted. Endpoints examined included length of stay (LOS), serious complications including Dressler's syndrome, sepsis, cerebrovascular accidents (CVA), and ventricular fibrillation, as well as overall inpatient mortality. Patients who develop aortic dissection were identified using ICD-9-CM code 441.0. The ICD-9-CM codes used to identify complication rates

were 411.0 for post-MI syndrome (Dressler's syndrome), 995.91 for sepsis, 434.91 for cerebrovascular accident, and 427.41 for ventricular fibrillation. Demographic and clinical characteristics as well as patient outcomes were compared across the two subgroups: patients who developed aortic dissection and those who did not. Categorical variables were compared using the *Chi*-square test, while continuous variables were compared using student t-test and analysis of variance (ANOVA). Multivariate analysis using the "backward Wald" method was performed to calculate odds ratios (OR) and determine independent factors which increased the risk of developing aortic dissection following PCI. All reported data was included in the calculations and analysis, including frequency and multivariate analysis. Any missing and unknown data were excluded. A *p*-value of <0.05 was utilized to determine statistical significance.

The current study was approved by the Saint Barnabas Medical Center Ethics Board. This is a retrospective study using data extracted from the NIS database. No specific patient identifiable information was utilized, and no patient consent form was required.

3. Results

777,595 patients underwent PCI for ACS as reported in the NIS database over the 11-year study period (2001-2011) (**Table 1**). There were 380 patients who experienced aortic dissection (0.05%) and 777,215 patients who did not (99.95%).

3.1. Demographic Characteristics

The mean age for all patients who underwent PCI for ACS was 64 ± 12 years (**Table 1**). Patients who developed aortic dissection after PCI had a significantly higher mean age (68 ± 12 years) than those who did not develop aortic dissection (64 ± 12 years), $p < 0.001$. A greater proportion of patients who developed aortic dissection after PCI were ≥ 65 years old (60.5% vs. 50.5%, $p < 0.001$), while a lower percentage of patients developing aortic dissection after PCI were < 50 years old (7.4% vs. 12.1%, $p = 0.004$) or between 50 and 64 years old (32.1% vs. 37.4%, $p = 0.004$). The majority of patients who developed aortic dissection were males (52.6%) with a male:female (M:F) ratio of 1.11:1, $p < 0.001$. While the majority of patients who did not develop aortic dissection were also males (66.2%), there was a significantly greater male preponderance with a M:F ratio of 1.96:1, $p < 0.001$. Among those who developed aortic dissection, 75.5% ($N = 234$) were Caucasian, 9.4% ($N = 29$) were African American, 9.7% ($N = 30$) were Hispanic, and 5.5% ($N = 17$) were designated as "other".

Overall, most patients who underwent PCI were admitted from the emergency room (ER) (34.2%) or transferred from another hospital (13.9%). A significantly greater proportion of patients who developed aortic dissection were admitted from the ER (41.5% vs. 34.2%, $p = 0.013$), compared to those who did not develop aortic dissection.

The majority of patients undergoing PCI for ACS had Medicare as primary

Table 1. Demographic Profile of 777,595 Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention (380 Patients who develop Aortic Dissection and 777,215 Patients who did not develop Aortic Dissection) from the Nationwide Inpatient Sample (NIS) Database (2001-2011).

Variables	Overall	Aortic Dissection	No Aortic Dissection	* <i>p-value</i>
Total, N (%)	777,595 (100.0%)	380 (0.05%)	777,215 (99.95%)	
Age, (Mean \pm SD)	64 \pm 12	68 \pm 12	64 \pm 12	<0.001
Under 50	94,364 (12.1%)	28 (7.4%)	94,336 (12.1%)	0.004
Age 50 to 64	290,770 (37.4%)	122 (32.1%)	290,648 (37.4%)	0.004
Age 65 and older	392,429 (50.5%)	230 (60.5%)	392,199 (50.5%)	<0.001
Gender				
Male	514,488 (66.2%)	200 (52.6%)	514,288 (66.2%)	<0.001
Female	263,071 (33.8%)	180 (47.4%)	262,891 (33.8%)	<0.001
Race, N (%)				
Caucasian	481,994 (79.1%)	234 (75.5%)	481,760 (79.1%)	0.870
African American	47,293 (7.8%)	29 (9.4%)	47,264 (7.8%)	0.924
Hispanic	40,617 (6.7%)	30 (9.7%)	40,587 (6.7%)	0.337
Other	39,230 (6.4%)	17 (5.5%)	39,213 (6.4%)	0.598
Admission source, N (%)				
ER	152,650 (34.2%)	88 (41.5%)	152,562 (34.2%)	0.013
Another hospital source	62,037 (13.9%)	37 (17.5%)	62,000 (13.9%)	0.102
Other health facility, including long-term care	12,672 (2.8%)	8 (3.8%)	12,664 (2.8%)	0.378
Court/Law enforcement	420 (0.1%)	0 (0.0%)	420 (0.1%)	
Routine, including births and other sources	218,318 (48.9%)	79 (37.3%)	218,239 (48.9%)	0.002
Primary expected payer, N (%)				
Medicare	393,835 (50.7%)	213 (56.2%)	393,622 (50.7%)	0.033
Medicaid	41,123 (5.3%)	30 (7.9%)	41,093 (5.3%)	0.023
Private insurance	278,791 (35.9%)	97 (25.6%)	278,694 (35.9%)	<0.001
Uninsured/Self pay	36,760 (4.7%)	24 (6.3%)	36,736 (4.7%)	<0.001
No charge	3577 (0.5%)	1 (0.3%)	3576 (0.5%)	0.571
Other	22,302 (2.9%)	14 (3.7%)	22,288 (2.9%)	0.338

Abbreviations: ER = emergency room; N = number; SD = standard deviation; **p*-value <0.05 was considered statistically significant.

insurance (50.7%), followed by private insurance (35.9%). More patients who developed aortic dissection were insured by Medicare (56.2% vs. 50.7%, $p = 0.033$), Medicaid (7.9% vs. 5.3%, $p = 0.023$), or uninsured/self-paying (6.3% vs. 4.7%, $p < 0.001$).

3.2. Clinical Characteristics

The most common indication for PCI was unstable angina (41.3%), followed by STEMI (36.3%), and NSTEMI (22.4%) (**Table 2**). More patients who developed aortic dissection had PCI done for unstable angina (48.4% vs. 41.3%, $p = 0.005$).

A greater percentage of patients who developed aortic dissection had preexisting comorbidities, such as peripheral vascular disease (PVD) (91.8% vs. 10.4%,

Table 2. Clinical Profile of 777,595 Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention (380 Patients who develop Aortic Dissection and 777,215 Patients who did not develop Aortic Dissection) from the Nationwide Inpatient Sample (NIS) Database (2001-2011).

Variables	Overall	Aortic Dissection	No Aortic Dissection	* <i>p-value</i>
Total, N (%)	777,595 (100.0%)	380 (0.05%)	777,215 (99.95%)	
Indication, N (%)				
STEMI	282,475 (36.3%)	123 (32.4%)	282,352 (36.3%)	0.109
NSTEMI	173,877 (22.4%)	73 (19.2%)	173,804 (22.4%)	0.140
Unstable angina	321,243 (41.3%)	184 (48.4%)	321,059 (41.3%)	0.005
Comorbidity, N (%)				
Anemia	59,054 (7.6%)	64 (16.8%)	58,990 (7.6%)	<0.001
Congestive heart failure	6898 (0.9%)	9 (2.4%)	6889 (0.9%)	0.002
Chronic pulmonary disease	117,106 (15.1%)	87 (22.9%)	117,019 (15.1%)	<0.001
Depression	39,284 (5.1%)	25 (6.6%)	39,259 (5.1%)	0.171
Diabetes, uncomplicated	224,635 (28.9%)	69 (18.2%)	224,566 (28.9%)	<0.001
Diabetes, with chronic complications	27,607 (3.6%)	15 (3.9%)	27,592 (3.6%)	0.676
Hypertension	537,983 (69.2%)	262 (68.9%)	537,721 (69.2%)	0.920
Hypothyroid	57,658 (7.4%)	37 (9.7%)	57,621 (7.4%)	0.084
Fluid and electrolyte disorder	62,827 (8.1%)	74 (19.5%)	62,753 (8.1%)	<0.001
Obesity	87,925 (11.3%)	33 (8.7%)	87,892 (11.3%)	0.106
Peripheral vascular disease	80,865 (10.4%)	349 (91.8%)	80,516 (10.4%)	<0.001
Renal failure	72,307 (9.3%)	61 (16.1%)	72,246 (9.3%)	<0.001

Abbreviations: N = number; NSTEMI = non-ST-elevation myocardial infarction; * p -value <0.05 was considered statistically significant; STEMI = ST-elevation myocardial infarction.

$p < 0.001$), fluid and electrolyte disorders (19.5% vs. 8.1%, $p < 0.001$), anemia (16.8% vs. 7.6%, $p < 0.001$), congestive heart failure (2.4% vs. 0.9%, $p = 0.002$), chronic pulmonary disease (22.9% vs. 15.1%, $p < 0.001$), and renal failure (16.1% vs. 9.3%, $p < 0.001$). In contrast, there were fewer patients with a history of uncomplicated diabetes (18.2% vs. 28.9%, $p < 0.001$).

3.3. Clinical Outcomes

Patients who developed aortic dissection had a longer LOS, compared to those who did not (9 ± 12 days vs. 3 ± 4 days, $p < 0.001$) (Table 3). Serious complications such as Dressler's syndrome (0.2%), sepsis (0.7%), and CVA (0.4%), were rare following PCI, however a greater percentage of patients who developed aortic dissection developed sepsis (2.9% vs. 0.7%, $p < 0.001$), CVA (2.4% vs. 0.4%, $p < 0.001$), and ventricular fibrillation (6.3% vs. 1.8%, $p < 0.001$).

The overall in-hospital mortality was significantly higher among patients who developed aortic dissection (13.2% vs. 1.4%, $p < 0.001$).

3.4. Multivariate Analysis

Multivariate analysis identified female gender (OR 1.5), Hispanic race (OR 1.9), uninsured/self-pay (OR 2.4), electrolyte disorders (OR 1.5), and PVD (OR 129.2) as independent risk factors for developing aortic dissection following PCI, $p < 0.05$.

Table 3. Clinical Outcome Profile of 777,595 Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention (380 Patients who develop Aortic Dissection and 777,215 Patients who did not develop Aortic Dissection) from the Nationwide Inpatient Sample (NIS) Database (2001-2011).

Variables	Overall	Aortic Dissection	No Aortic Dissection	* <i>p</i> -value
Total, N (%)	777,595 (100.0%)	380 (0.05%)	777,215 (99.95%)	
Length of stay (mean days \pm SD)	3 ± 4	9 ± 12	3 ± 4	<0.001
Serious complication, N (%)				
Dressler's syndrome	1404 (0.2%)	1 (0.3%)	1403 (0.2%)	0.704
Sepsis	5221 (0.7%)	11 (2.9%)	5210 (0.7%)	<0.001
CVA	3465 (0.4%)	9 (2.4%)	3456 (0.4%)	<0.001
Ventricular fibrillation	14,337 (1.8%)	24 (6.3%)	14,313 (1.8%)	<0.001
Outcome of hospitalization, N (%)				
Alive	766,205 (98.6%)	329 (86.8%)	765,876 (98.6%)	<0.001
Dead	11,258 (1.4%)	50 (13.2%)	11,208 (1.4%)	<0.001

Abbreviations: CVA = cerebrovascular accident; N = number; SD = standard deviation; * p -value <0.05 was considered statistically significant.

4. Discussion

Aortic dissection is a rare complication following PCI. Although PCI was not performed until 1977, iatrogenic aortic dissection following open-heart surgery was first reported in the 1960s [6] [7]. In a recent single-center retrospective study over a 14-year period published by Leontyev *et al.* (2012), the incidence of iatrogenic aortic dissection was reported to be 0.06% following other cardiac surgical procedures and 0.01% following cardiac catheterization procedures [3]. In the current study, aortic dissections occurred in 0.05% of the PCI cases following ACS with an in-house mortality of 13.2%. These results are consistent with more recent PCI studies, which have reported incidence rates ranging from 0.02% to 0.07%, with mortality rates as high as 50% [8] [9] [10] [11] [12]. Patients who develop aortic dissections following PCI had longer lengths of hospitalization and lower survival rates. Moreover, these patients were more likely to have other serious complications associated with PCI, including sepsis, CVA, and ventricular fibrillation. Although a rare complication; the incidence and clinical implications of aortic dissection after PCI warrants further investigation given the high mortality rate and the growing number of cardiovascular intervention procedures performed [3] [4] [5]. This is the largest retrospective cohort study to delineate the demographic and risk factors among PCI patients who develop aortic dissection.

The exact mechanism of aortic dissection following PCI remains unclear; however, several possible mechanisms have been proposed, with the most common being retrograde propagation of a coronary dissection secondary to mechanical trauma of a wire, catheter, balloon inflation, or another interventional device and trauma resulting from the guiding catheter itself [2] [12] [13]. Previous studies have shown an association between atherosclerosis and heavily calcified vessels with increased risk of catheter-induced aortic dissection [2] [14] [15] [16]. The relationship between the role of atherosclerosis and the velocity of the retrograde flow, more specifically a forceful contrast injection into the false lumen, has been suggested as an additional or concurrent mechanism for aortic dissection following PCI [10]. A high velocity retrograde jet may disrupt diseased intima at the tip of the cannula at the time of cannulation or later during the perfusion [7].

Aortic dissection after PCI is more prevalent in patients >65 years old. This data is consistent with several studies on aortic dissection, which have reported older age as a risk factor [17] [18]. In addition, there were a greater proportion of females, African Americans, and Hispanics who developed aortic dissection after PCI. Females and Hispanics were at a 1.5 and 1.9 times greater risk of developing aortic dissection following PCI. This is in contrast to a retrospective study by Nienbaber *et al.* involving 1078 patients enrolled in the International Registry of Acute Aortic Dissection (IRAD), which reported that aortic dissections were less frequent in females, however, females who did develop aortic dissection were significantly older than men [19]. These findings suggest there should be a greater suspicion for the possibility of aortic dissection following

PCI in these high-risk patients.

In addition to age and gender, the implication of PVD in the incidence of aortic dissection following PCI has been discussed. Patients with PVD had a 129.2 times higher chance of developing aortic dissection. In a study of 48 patients who developed aortic dissection following PCI by Leontyev *et al.*, 22.9% of patients had a history of PVD [3]. In addition to PVD being a risk factor for aortic dissection, 47.9% of patients had New York Heart Association (NYHA) class III/IV symptoms, and 33.3% of patients had a left ventricular ejection fraction (LVEF) <50% [3]. Multivariate analysis indicated coronary malperfusion and preoperative NYHA class IV symptoms as being independently associated with early mortality [3].

Diagnostic imaging for aortic dissection is used to rapidly confirm or exclude the diagnosis, and classify the extent of the dissection. Computed tomography (CT) is used in 61% of cases, while echocardiogram is used in 33%, magnetic resonance imaging (MRI) in 4%, and aortography in 4% [14] [20] [21]. Transthoracic echocardiography (TTE) can be beneficial in identifying proximal aortic dissections in emergent cases with unstable patients, and confirmation of the diagnosis often requires more than one non-invasive imaging study [14].

In addition to current imaging, the diagnostic biomarkers which permit the early detection of aortic dissection have been investigated. Circulating smooth muscle myosin heavy chain protein, which is released from damaged medial smooth muscle of the aorta, has been shown to be elevated in the initial hours of an acute dissection [14] [22]. In a review studying the circulating biomarkers available for the diagnosis and prognosis stratification of aortic dissection, Morrello *et al.* (2014) reported that the variation in the range of biomarkers of aortic dissection could potentially be used as a tool to screen symptomatic patients, to identify patients at higher risk of aortic disease, to rule out aortic dissection with low clinical probability of aortic dissection and/or to obtain prognostic stratification of affected patients [22]. Acute phase reactors such as C-reactive protein, fibrinogen, D-dimer, and soluble elastin fragments have all been evaluated and serve as additional diagnostic tools in determining disease extent and progression [14] [22] [23].

Treatment of acute aortic dissections typically involves both medical and surgical management, depending upon the location of the dissection. Treatment choice is determined based on patient stability, nature of the dissection involving the coronary artery, and extent of aortic dissection [2]. Dissections involving the ascending aorta are surgical emergencies requiring quick open or endovascular repair and reconstruction to improve prognosis [14]. In contrast, dissections involving the descending aorta can be treated medically unless there are indications of progression of the dissection, intractable pain, organ malperfusion, or extra-aortic blood is demonstrated [14] [20]. While surgical resection or stenting of the ascending aorta and possibly the aortic arch is considered the gold standard treatment for dissections involving the ascending aorta; this has also been extended to patients with iatrogenic aortic dissections [24].

In this study, aortic dissections occurred most often following PCI for unstable angina compared to STEMI and NSTEMI. The decrease in incidence and mortality rate after aortic dissection following PCI reported in the current study may be attributable to improved recognition of aortic dissection as a complication after PCI and advancements in PCI procedures [3]. Drug-eluting stents, have been shown to significantly reduce the rate of in-stent revascularization, but has been associated with increased rates of late stent thrombosis [25]. Bangalore *et al.* (2013) completed a meta-analysis, which included 28 randomized control trials with 34,068 patients, evaluating the long-term efficacy and safety of drug-eluting stents versus bare-metal stents in patients with STEMI. Results showed that drug-eluting stents reduced the risk of total vessel revascularization by over 30% without increasing the rate of adverse events [26]. Leontyev *et al.* estimated a mean survival of 4.3 ± 0.9 years, and survival at 1-, 3-, and 5-year post-iatrogenic aortic dissection repair to be $43\% \pm 7\%$, $40\% \pm 4\%$, and $40\% \pm 7\%$, respectively [3]. Hence, the continuation of advancements in the area of PCI and ACS treatment coupled with the identification of risk factors associated with aortic dissection following PCI are critical to improve the prognosis of the patient population at risk.

Given the retrospective nature of this study, the current study has several limitations which are inherent to large administrative databases, including sampling and coding errors. Complications occurring immediately following the procedure were reported in the NIS database; however, readmissions for a complication of undergoing PCI were not identifiable, potentially underestimating the actual complication rates. These limitations however, would apply to all groups and therefore should not have affected the overall results of this study. This limitation to in-hospital information without follow-up data could lead to long-term complications and mortality after hospital discharge not being captured in this study. Data regarding specific procedural characteristics, the specific and extent of each vessel involvement, vascular access route, catheters used, and operator experience was also lacking. Furthermore, the presence of comorbidities was based on the presence of administrative codes within the NIS database and was not clinically confirmed. Participation in the NIS database is voluntary, and only selected centers participate in the registry. Further, there is no information regarding the method of diagnosing aortic dissection, the location and extent of dissection, whether or not the carotid artery was dissected, timing of surgery relative to the qualifying event, and the management or medications given to the patients. Despite these limitations however, the NIS includes data from 1000 different hospitals in the US and more than 700,000 patient records were obtained for this study, and is likely a diverse enough sample to be able to generalize across most US hospitals in terms of delivery of care.

5. Conclusion

Aortic dissection is a rare but potentially lethal complication after PCI for ACS, which occurs most commonly in older patients admitted from the ER with Me-

dicaid insurance. Aortic dissection is associated with significantly worse outcomes including longer lengths of stay, and higher rates of mortality, ventricular fibrillation, sepsis, and CVA. Hispanics, females, uninsured/self-paying patients and those with electrolyte disorders or PVD are at the highest risk of aortic dissection. Despite new advances in diagnosing and aggressive and timely treatment, aortic dissection after PCI is associated with significant morbidity and mortality. This report represents the largest published study to examine trends in demographic and clinical profiles of patients who develop aortic dissection following PCI. The current study gives insight into the existing risk factors, which predisposes patients to the development of aortic dissection after PCI. In addition, the implications of aggressive manipulation of a guide catheter along with high velocity retrograde flow should be stressed to operators as significant factors in the incidence of aortic dissection after PCI in the population at risk. Knowledge of key diagnostic biomarkers and imaging studies is necessary to facilitate the urgent diagnosis and treatment of aortic dissection following PCI and to prevent morbidity and mortality. Clinicians should be more cognizant of patients at increased risk of developing aortic dissection in order to institute earlier screening in high-risk patients.

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Abbreviations

ACS: Acute coronary syndrome
AHRQ: Agency for Healthcare Research and Quality
ANOVA: Analysis of variance
CT: Computed tomography
CVA: Cerebrovascular accidents
HCUP: Healthcare Cost and Utilization Project
IRAD: International Registry of Acute Aortic Dissection
LOS: Length of stay
LVEF: Left ventricular ejection fraction
MI: Myocardial infarction
MRI: Magnetic resonance imaging
NIS: Nationwide Inpatient Sample
NSTEMI: Non-ST-elevation myocardial infarction
OR: Odds ratios
PCI: Percutaneous coronary intervention
PVD: Peripheral vascular disease
STEMI: ST-elevation myocardial infarction
TTE: Transthoracic echocardiography



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Thiol-Disulfide Homeostasis in Patients with Panic Disorder

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Abstract

Objective: To determine serum thiol/disulfide homeostasis in panic disorder (PD). **Methods:** Serum native thiol, total thiol, and disulfide levels were measured in the patients with 40 PD patients and 40 healthy subjects. Serum native thiol, total thiol, and disulfide levels were measured with a novel colorimetric, automated method. The thiol-disulfide ratio was also calculated. **Results:** The native thiol ($p < 0.001$) and total thiol ($p < 0.001$) levels, and the native thiol/total thiol ($p < 0.001$) ratio were significantly lower, whereas disulfide/native thiol ($p < 0.001$) and disulfide/total thiol ($p < 0.001$) ratio significantly increased in the PD patient group compared to the control group. The cut-off value was 92.26, 3.83 and 3.56 for native thiol/total thiol, disulfide/native thiol and disulfide/total thiol respectively. **Conclusion:** This is the first study in the literature to evaluate thiol-disulfide homeostasis in patients with PD. Our results suggest that the disulfide/thiol ratio is significantly greater in panic disorder patients.

Keywords

Panic Disorder, Thiol-Disulphide Homeostasis

1. Introduction

Despite significant progress in studies on PD, etiopathogenic processes cannot be clearly defined. One of the important processes in the pathogenesis of PD is oxidative stress [1]. Oxidative stress can be described as the impairment of cell membrane functions due to the disequilibrium between the free oxygen radicals and the antioxidant mechanisms. Oxidative stress can be evaluated indirectly by the measurement of some antioxidant enzyme levels such as superoxide dismutase (SOD), catalase (CAT), or glutathione peroxidase (GSH-Px), by-products of lipid peroxidation such as malondialdehyde (MDA) [2]. Although many impor-

tant findings have been revealed by studies on oxidative and anti-oxidative parameters (MDA, SOD, glutathione (GSH), adenosine deaminase (ADA), xanthine oxidase (XO), total antioxidant status (TAS), total oxidative status (TOS), oxidative stress index (OSI), ceruloplasmin) related to PD etiology, oxidant-antioxidant homeostasis of PD is not fully clear [1] [3] [4].

The thiol groups are the primary targets of the reactive oxygen species. Thiol is an organic compound containing sulfhydryl (-SH) group which has a critical role in preventing the occurrence of oxidative stress. Thiol groups are oxidized by reactive oxygen species and reversible disulfide bonds are formed. This is the earliest sign of protein oxidation [5] [6] [7]. The most of thiols in plasma are formed by albumin, and the remaining part of the thiols consists of low molecular weighted thiols such as homocysteine, methionine, cysteine, cysteinyl glycine, glutathione, and γ -glutamylcysteine [8]. Thiol groups of proteins are oxidized by oxidant molecules and reversibly converted to disulfide bond structure. Disulfide bond structure can be again reduced to the thiol group. Maintenance of the thiol-disulfide homeostasis is kept by conversion of disulfide bond structure to the thiol group. When the native thiol levels decrease, disulfide levels increase [9].

Thiol-disulfide homeostasis has an important role on antioxidant protection, detoxification, apoptosis, stabilization of protein structure, regulation of protein function, cell signaling and transcription [6]. While only the thiol levels were able to be measured since 1979, a novel and colorimetric, automated method was developed by Erel and Neselioglu so that the thiol and also the disulfide levels can be measured one by one [9] [10]. Abnormal thiol-disulfide homeostasis state is related to the pathogenesis of different diseases, including diabetes mellitus [11], cardiovascular diseases [12], cancers [13], neurological diseases [14] [15], liver diseases [16] and chronic renal failure [17].

There is no study in the literature showing the relationship between PD with the thiol-disulfide homeostasis. The aim of our study is to investigate the thiol-disulfide homeostasis in patients with PD.

2. Material and Method

Totally 80 volunteers; 40 (15 males, 25 females) PD patients and 40 (20 males, 20 females) healthy controls aged between 18 - 65 years old, were participated into study. Informed consent was obtained from the patient and control groups. The PD patients were enrolled at the first admission, to the psychiatry clinic of Antalya Education and Research Hospital, between July 2016 and October 2016, and had no treatment, were diagnosed according to the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [18] Control group was recruited from healthy persons who were hospital staff and were assessed by a semi structured psychiatric interview. The study complied with the Declaration of Helsinki, and was approved by institutional ethics committee of Antalya Training and Research Hospital.

Patients were excluded from the study if they met one or more of the follow-

ing criteria: hypertension, heart and cerebrovascular disease, diabetes mellitus, hepatic or renal failure, autoimmune diseases, active infection, active or chronic inflammatory diseases, smoking, obesity, collagen tissue disease and treatment with antiinflammatory, antioxidant or immunosuppressive medications, malignancy, alcohol and substance abuse or dependence, vitamin supplements. Sociodemographic data form was completed to the participants.

Antecubital vein blood was taken after 12 hours of fasting from the participant. Vacutainer gel tubes were used. Serum was separated by centrifugation 10 min at 4000 rpm, at 4°C and rapidly serum fractions were stored at -80°C.

A new and fully colorimetric automated method developed by Erel *et al.* was used for the measurement of plasma native thiol, total thiol and disulfide levels based on the reduction of dynamic disulfide bonds to functional thiol groups. Native thiol content was subtracted from the total thiol content; half of the obtained difference provides the disulfide bond quantity. Disulfide/thiol ratio, disulfide/total thiol ratio and thiol/total thiol ratios were calculated automatically [9].

3. Statistical Analysis

In the statistical evaluation of the data, the statistics package for social sciences (SPSS) Version 18.0 computer package program was used. The results were presented as mean \pm SD. The differences between groups were determined by student's unpaired *t*-test and Mann Whitney U-test. Pearson correlation coefficient was used to assess correlations. Distribution of continuous variables was assessed with Kolmogorov-Smirnov. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off levels of native thiol, total thiol, disulfide/native thiol and disulfide/total thiol. Using the ROC curve, the responsiveness is described in terms of sensitivity and specificity. Values for sensitivity and for false-positive rates (1-specificity) are plotted on the *y*- and the *x*-axes of the curve and the area under the curve represents the probability a measure correctly classifies patients as improved or unchanged. P values less than 0.05 was accepted as the significance level.

4. Results

The mean ages among the PD group (15 male, 37.5%) were 39.9 ± 14.4 years, and the mean ages of the control group (20 male, 50%) were 38.2 ± 13.6 years. The age and gender distributions were similar in both groups ($p = 0.594, 0.260$, respectively).

The laboratory findings of the control and PD groups are in **Table 1**. Native and total thiol levels were significantly lower among the PD group relative to the control group ($p < 0.001$). There was no significant difference between the control and the PD groups in terms of disulfide levels ($p = 0.261$). While the native thiol/total thiol ratio was decreased in the patient group ($p < 0.001$), disulfide/native thiol and disulfide/total thiol ratios were elevated in the patient group ($p < 0.001, p < 0.001$ respectively).

ROC analysis of area under the curve, cut-off levels, and sensitivity and specificity values are given in **Table 2**. The AUC for the Native Thiol and Native Thiol/Total Thiol ratio were 0.855 and 0.793 respectively.

ROC analysis was used. ROC curves of all parameters are seen in **Figure 1**. The sensitivity and specificity of Total Thiol were 80% and 87.5%, respectively, and the AUC was 0.837.

5. Discussion

The relationship of oxidative stress between PD was demonstrated in different studies. Several studies conducted in patients with PD related to oxidative stress have evaluated molecules such as MDA, SOD, GSH, CAT, nitric oxide (NO), uric acid, and paraoxonase (PON); however, more recent studies have also evaluated distinct parameters, such as TAS, TOS, and OSI [1] [3] [4]. These studies have yielded variable results.

In a study done by Gul *et al.*, the oxidant (MDA) was found higher and antioxidant (total antioxidant capacity (TAC), PON, arylesterase (ARE)) levels lower in PD patients compared to the control group [3]. Otherwise Kuloglu *et al.*,

Table 1. Comparison of the laboratory findings between the control group and PD group.

	Patient Group (n = 40) Mean ± SD	Control Group (n = 40) Mean ± SD	p
Native Thiol (μmol/l)	302.90 ± 90.95	413.66 ± 46.27	<0.001*
Total Thiol (μmol/l)	333.70 ± 92.18	442.09 ± 48.63	<0.001*
Disulfide (μmol/l)	15.40 ± 3.23	14.22 ± 5.77	0.261
Disulfide/Native Thiol (%)	5.67 ± 2.63	3.47 ± 1.46	<0.001*
Disulfide/Total Thiol (%)	5.00 ± 1.96	3.22 ± 1.26	<0.001*
Native Thiol/Total Thiol (%)	90.00 ± 3.92	93.57 ± 2.53	<0.001*

*Correlation is significant at the 0.05 level (2-tailed). Students t test was used.

Table 2. ROC analysis data of Native Thiol, Total Thiol, Disulfide, Disulfide/Native Thiol, Disulfide/Total Thiol, Native Thiol/Total Thiol parameters.

Biomarker	Area Under Curve (AUC)	P value	Cut-off level	Sensitivity (%)	Specificity (%)	+LR	-LR
Native Thiol	0.855	<0.001	353.1	75.00	92.50	10.0	0.27
Total Thiol	0.837	<0.001	393.8	80.00	87.50	6.40	0.23
Disulfide	0.579	0.233	10.6	97.50	32.50	1.44	0.07
Disulfide/Native Thiol	0.793	<0.001	3.83	82.50	65.00	2.36	0.27
Disulfide/Total Thiol	0.793	<0.001	3.56	82.50	65.00	2.36	0.27
Native Thiol/Total Thiol	0.793	<0.001	92.26	77.50	70.00	2.58	0.32

+LR = Positive likelihood ratio; -LR = Negative likelihood ratio.

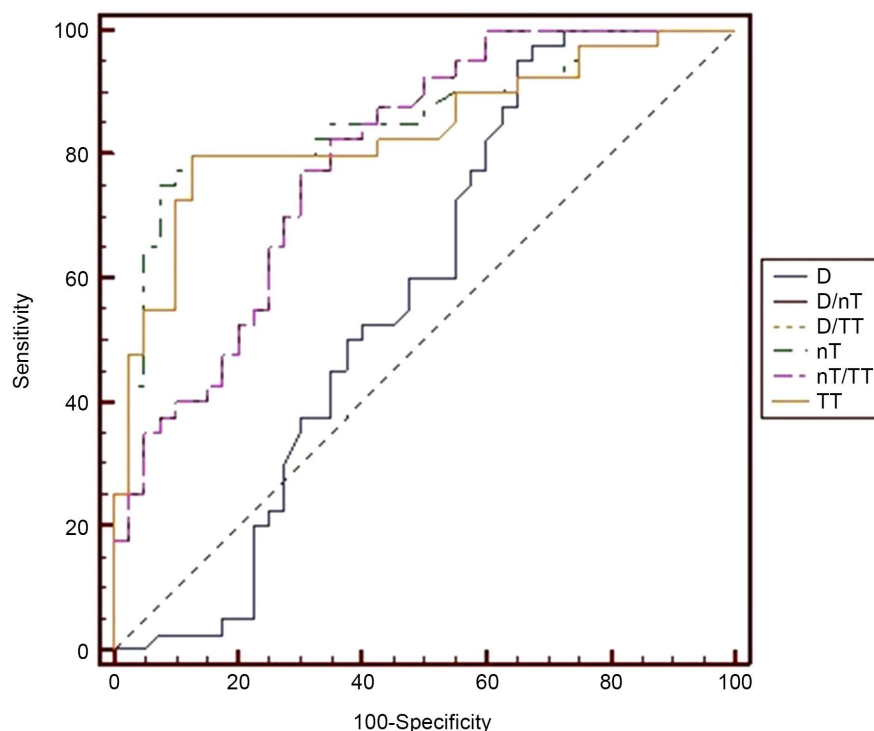


Figure 1. ROC analysis of PD patients versus controls.

found the GSH-Px, SOD and MDA levels to be significantly higher in the PD group compared to the control group [19]. Another study has again evaluated oxidative and anti-oxidative parameters in PD. Oxidants (adenosine deaminase (ADA) and XO levels) were higher in the patient group than the control group in this study but there was no significant difference regarding antioxidant parameters [20]. Although many important findings have been revealed by studies on oxidative and anti-oxidative PD etiology [19] [20], oxidant-antioxidant homeostasis of PD has not been fully elucidated, yet.

The thiol-disulfide homeostasis plays a role in the cellular functions. The thiols are the primary target for oxygen radicals which are non-enzymatic anti-oxidant molecules taking an important part in preventing damage caused by free radicals [21]. The extent to which the proteins are affected from free radicals is related to their amino acid content. Molecules containing unsaturated bonds and SH groups and proteins releasing amino acids such as homocysteine, methionine, cysteine, tryptophan, tyrosine, phenylalanine, and histidine can be more easily affected by free radicals [22] [23]. Thiol-disulfide homeostasis, which was first measured in 1979, could be only measured in one direction [10]; however, a novel, automated and colorimetric method developed in 2014 by Erel *et al.* which allows the measurement of the homeostasis in either direction. Erel *et al.* reported that disulfide levels were higher in patients with diseases such as diabetes, in smokers, obese patients, premature ovarian failure, subclinical hypothyroidism and were lower in patients with proliferative diseases, such as urinary bladder cancer, renal cancer, non-small cell lung cancer and multiple myeloma [9].

This is the first study in the literature to evaluate thiol-disulfide homeostasis in patients with PD. The present study found decreased levels of native thiol, total thiol, and native thiol/total thiol ratio and increased disulfide/native thiol and disulfide/total thiol levels in the patient group, compared to the control group. These findings suggest that thiol-disulfide homeostasis has shifted toward disulfide direction in PD patients. Decreased thiol levels indicate a problem in anti-oxidant system in PD patients. According to our data, the cut-off value was 353.1 $\mu\text{mol/L}$, 393.8 $\mu\text{mol/L}$, 92.26 (%), 3.83 and 3.56 for native thiol, total thiol, native thiol/total thiol, disulfide/native thiol and disulfide/total thiol level respectively. The patients with serum native thiol, total thiol and native thiol/total thiol levels below these thresholds must be particularly evaluated for PD. The evaluation can be made by the automated measurement of these values.

Although the increase in disulfide molecules generated by oxidation of thiol groups in the patient group was not statistically significant, increased disulfide/native thiol and disulfide/total thiol levels suggested increased oxidative stress in PD patients. The deficiency of a significant increase in disulfide levels in the PD group can be explained by the lack of stability in the thiol-disulfide homeostasis and the fact that this balance is affected by kidney and liver functions [24].

This study is cross sectional so we think that this is the main limitation. The sample size of the patient and control groups may be another limitation.

6. Conclusion

The present study investigated thiol-disulfide homeostasis using a new, colorimetric, and automated method in PD patients. Our study results showed that serum thiol levels were lower and disulfide/total thiol levels were higher in PD patients, compared to the controls. These findings also highlight the importance of oxidative stress in the etiopathogenesis of PD. We believe that further studies investigating the effects of SH-containing anti-oxidant components on thiol-disulfide homeostasis and clinical outcomes of PD treatment would make significant contribution to the treatment of this disease.

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Beliefs and Clinical Practice for Complex Regional Pain Syndrome (CRPS) Managed by Physiotherapists on the South Island of New Zealand

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Abstract

On the South Island of New Zealand, Anaesthetists and other Medical Professionals, frequently refer their patients with Complex Regional Pain Syndrome (CRPS) for physiotherapy management. Beliefs about what is important for the management of patients with CRPS are lacking across all medical and allied health disciplines. Difficulties in diagnosis and evidence for intervention methods is moderate or can be conflicting. This paper explores what Physiotherapists believe to be important in a clinical setting for their management of CRPS, as well as documenting and evaluating their interventional methods used in everyday clinical practice across the region of the South Island of New Zealand. This has not been recorded before. Eighty-one Physiotherapists replied to questions on their usual treatment interventions for the management of CRPS, their frequency of use of these treatment interventions, and what they believed to be important in the management of pain and improvement of function. The results demonstrated that CRPS is not a common condition seen regularly by Physiotherapists; that there is a high level of variation between the physiotherapy interventions used and that Physiotherapists' beliefs regarding interventions used for pain management and functional restoration differ. Education was reported as the most frequently used intervention method. Those physiotherapists seeing CRPS patients more frequently are more likely to use evidence based intervention methods like graded motor imagery or sensory motor training.

Keywords

Physiotherapy, Anaesthetists in Pain Management, Complex Regional Pain Syndrome (CRPS), Beliefs, Management, Intervention Methods, Outcomes

1. Introduction

Complex Regional Pain Syndrome (CRPS) is a persistent pain syndrome with a low prevalence [1] [2] which exhibits abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings and shows variable progression over time [3] [4] [5] [6]. It is evaluated by anaesthetists in Pain Management or by physiotherapists. It can be argued that it is both under-diagnosed [7] and over-diagnosed [8] [9]. Early diagnosis and referral by anaesthetists in Pain Management or by other medical disciplines to physiotherapists is regarded as essential [10]. Unresolved issues remain. There is no gold standard for the management of CRPS. Contrasting interventional methods exist in the literature around improving functional ability or controlling the pain experience. Beliefs about what is important or not for the management of CRPS remain unknown.

In other domains, beliefs held by Medical Practitioners and Allied Health Professionals are shown to affect practice, for example, as follows: the pain experienced in the elderly can be minimised [11]; physiotherapists will continue to treat low back despite any evidence of improvement [12]; and beliefs about opioid medication affect prescription practice [13] [14].

Amongst physiotherapists two opposing beliefs exist regarding pain modulation or pain exposure. Pain modulation is supported by the evidence for Graded Motor Imagery (GMI) [15] [16], mirror exercise [17], Sensory-Motor Training (SMT) [18], Graded Exposure (GEXP) [19], relaxation [20], psychological techniques [21] and Transcutaneous Nerve Stimulation (TENS) [22]. Pain Exposure (PEXP) is supported by the evidence for progressive exercise loading without analgesia moving towards restoration of function [15] [23] [24]. The beliefs of Medical Practitioners or Allied Health Professionals on the management of CRPS are not documented.

2. Purpose

Beliefs about what Physiotherapists in a clinical setting regard as important for their management of CRPS, as well as their beliefs about the interventional methods used in everyday clinical practice across the region of the South Island of New Zealand were evaluated.

3. Method

There are 150 private practices and hospital outpatient departments listed across the South Island of New Zealand by the New Zealand Physiotherapy Society (PNZ). Physiotherapy staff numbers in these practices or clinics vary from solo practitioners to those with high staff numbers. Each individual practice or clinic was contacted to find out whether they accepted CRPS patients or not. Those accepting CRPS patients were asked to fill in a paper-based questionnaire about their usual physiotherapy management for CRPS, and what they believed to be important in the management of pain and for the function in these patients. Ethical approval for this study was provided by the University of Otago Ethics

committee (Reference number H13/103). Inclusion criteria were a registered Physiotherapist currently working in any setting on the South Island of New Zealand who also accepted treating CRPS patients. Exclusion criteria were a registered Physiotherapist who never saw CRPS patients.

The questionnaire given to the Physiotherapist contained four sections. The first section asked how frequently CRPS patients were treated by them. A Likert Scale containing the following information was used: never; seldom (2 - 5 times per year); occasionally (5 - 10 times a year); regularly (2 - 3 times per month); or often (more than 5 times per month). The second section asked about the precise interventions carried out and their frequency of use. A Likert scale containing the following information was used, such as: never use this; occasionally use this; often use this; or most often use this. The third section enquired about what unlisted interventions the Physiotherapist used and their frequency of use. The fourth section looked at the beliefs the Physiotherapist held about the management of CRPS. The belief choice was as follows: reducing the pain is essential to improve the function; improving the function is essential to reduce the pain; exercising and increasing pain is contra-indicated; and exercising and increasing pain is indicated.

4. Statistical Analysis

Standard descriptive statistics (Statistica 7, Microsoft Excel for windows PC) was used to compare categorical variables. Data analysis used ANOVA tests for significance between categorical variables and frequency of consultations with Physiotherapists.

5. Results

The 64 clinics and hospital outpatient departments who accepted patients with CRPS employed a total of 141 Physiotherapists. The 84 clinics and hospital outpatient departments who did not accept CRPS patients were excluded from the sample. Questionnaires were posted in self-addressed and pre-stamped envelopes (one for each Physiotherapist), or personally delivered. Eighty-one Physiotherapists answered the questionnaire and returned it either personally ($n = 5$) or by mail ($n = 76$). This provided a response rate of 57%. Participation rate in the physiotherapy intervention questionnaire is shown in **Figure 1**.

Eighty six (57.3%) of the 150 physiotherapy practices or outpatient clinics contacted never accepted any CRPS patients and were not asked to participate in the study. The 81 Physiotherapists who treated patients with CRPS came from 64 (or 43%) of the clinics and hospital outpatient departments across the South Island of New Zealand. Seven (or 4%) of the 150 clinics contacted accepted patients with CRPS declined to answer the questionnaire. Reasons given were as follows: no reason given ($n = 1$); about to retire ($n = 1$); staff shortages ($n = 1$); unwilling to have practice scrutinised ($n = 2$); too busy ($n = 1$); or an assessment only service ($n = 1$).

Sixty-three per cent of this sample of Physiotherapists on the South Island

who accepted patients with CRPS treated them infrequently (2 to 5 times annually). Twenty per cent treated 5 to 10 CRPS patients annually. Only 1% of Physiotherapists treated more than 5 CRPS patients in a month; 9% of Physiotherapists treated 2 - 3 CRPS patients each month. These data were simplified into two categories. Ninety per cent of Physiotherapists were categorised as seldom treating CRPS patients (less than 2 CRPS patients per month). Ten per cent of Physiotherapists were categorised as more frequently treating CRPS patients (more than 2 CRPS patients per month).

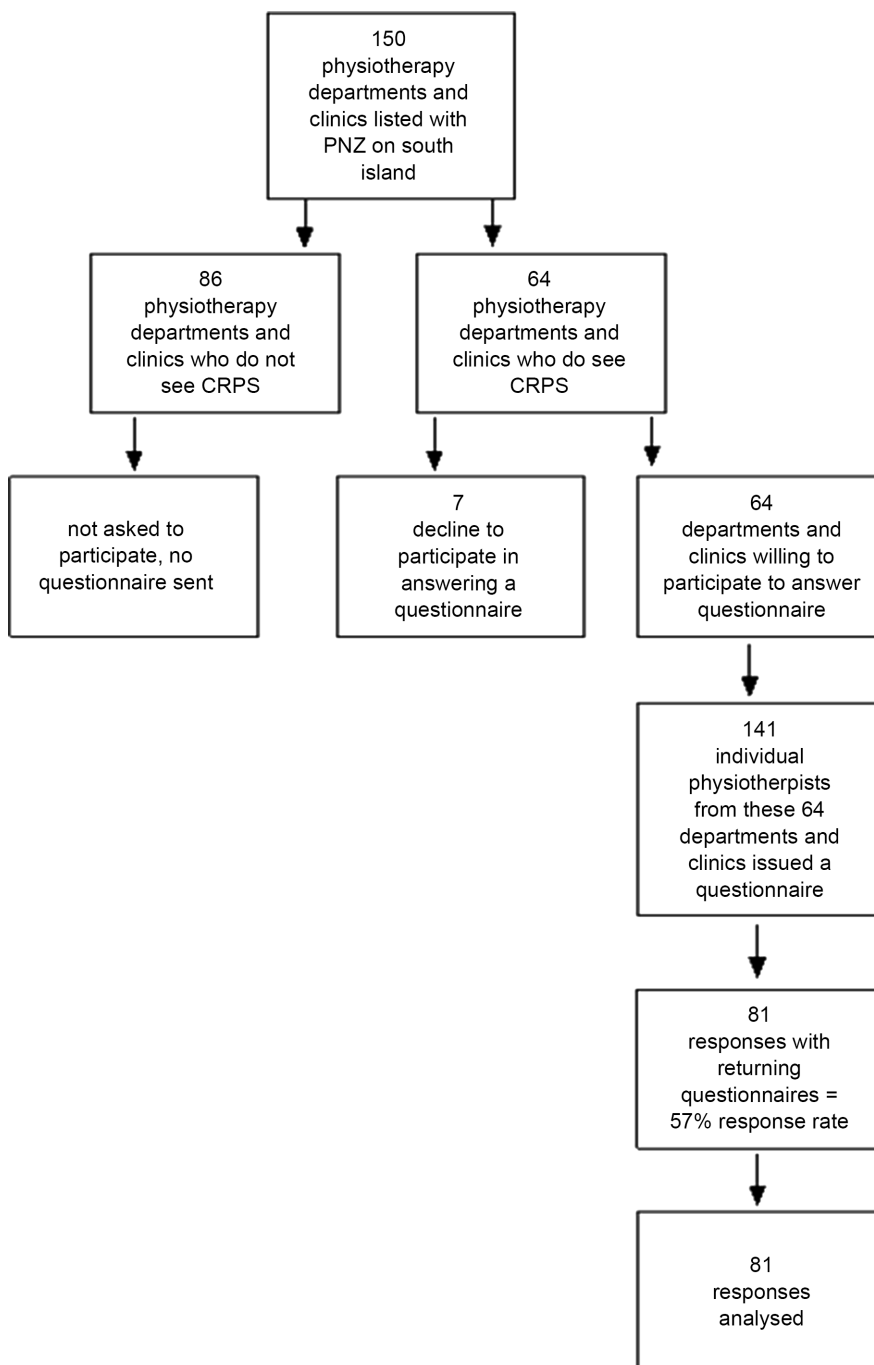


Figure 1. Participation with the physiotherapy intervention questionnaire.

The routine physiotherapy interventions examined were as follows: active exercises within pain limits; active exercises despite pain; resisted exercises despite pain; eccentric exercises; pain exposure exercises; graded exposure exercises; education; passive exercises within pain limits; passive exercises despite pain; pool exercises; neural stretches; tendon glides; balance exercises; proprioceptive exercises; lymphoedema massage; oedema massage; prescribed homework; scheduled as time contingent or pain contingent; sensory mapping training; discrimination training; desensitising training; GMI in classic order; GMI in ad hoc order; mirror exercises; prism exercises; relaxation exercises; breathing control; cognitive techniques for pain control; problem solving techniques for pain control; cognitive behavioural therapy (CBT); acceptance and commitment therapy (ACT); iontophoresis; soft tissue mobilisation; trigger point release; and other interventions (not listed). Fifteen Physiotherapists used acupuncture.

Education was the modality most commonly used as an intervention for CRPS (83% of Physiotherapists). Proprioceptive training and desensitising were often used (58% of the Physiotherapists). Forty nine percent of physiotherapists applied active exercise despite pain occasionally; active and resisted exercises within pain limits were used by 41% and 42% of the Physiotherapists, respectively. The types of interventions listed as occasionally used by the largest groups were trigger points release (53%), active exercise despite pain (49%), pool exercise (44%), and soft tissue mobilisation (41%). On the other hand, Physiotherapists (88%) seldom used iontophoresis, acupuncture (81%), prism exercise (78%), or acceptance and commitment therapy (70%).

The frequency of use of all interventions used is listed in **Table 1**.

In the group who mostly used GMI, 10% used it in the classic order versus 2% who used it in an ad hoc sequence. However, 43% never used a GMI classic sequence at all. Twenty per cent occasionally used the GMI classic sequence. Fifteen percent of the GMI users often applied the classic sequence. Ten percent of Physiotherapists used the classic sequence of GMI as the most common intervention. Those who used the ad hoc sequence showed similar figures. This is shown in **Figure 2**.

These data were further analysed using ANOVA tests for significance to determine if the frequency of seeing CRPS patients affected the type of intervention used. The more frequently a Physiotherapist evaluated CRPS patients, the following occurred, namely: 1) they used GMI more often rather than occasionally in the classic order of the 3 phases, $p = 0.017$; 2) the more they used relaxation techniques often rather than occasionally, $p = 0.021$; 3) the more likely they were to use SMT, and sensory mapping or discrimination occasionally rather than never, $p < 0.001$ and; 4) the more often they used oedema massage rather than seldom, $p = 0.029$. **Table 2** outlines the significant differences between those Physiotherapists who evaluated CRPS patients frequently compared to those who seldom saw CRPS patients.

Table 1. Physiotherapy interventions for CRPS and frequency of use.

Intervention method	Answered question	Frequency of use by Physiotherapist (% valid answers)			
	N (%)	Never	Occasionally	Often	Mostly
Active exercise within pain limit	77 (95%)	0%	14%	41%	41%
Active exercise despite pain	76 (94%)	20%	49%	20%	5%
Resisted exercise within pain limit	74 (91%)	2%	33%	42%	14%
Resisted exercise despite pain	73 (89%)	38%	40%	11%	0%
Eccentric exercise	72 (89%)	38%	40%	11%	0%
Pain exposure exercise	65 (80%)	30%	32%	11%	7%
Graded exposure exercise	69 (85%)	11%	20%	33%	21%
Education	79 (98%)	0%	1%	14%	83%
Passive exercise within pain limits	71 (88%)	9%	32%	30%	17%
Passive exercise despite pain	71 (88%)	36%	37%	11%	2%
Pool exercise	76 (94%)	22%	44%	20%	7%
Neural stretches	72 (91%)	11%	43%	33%	4%
Tendon glides	72 (91%)	19%	36%	32%	2%
Balance exercise	73 (89%)	9%	22%	51%	9%
Proprioceptive Exc	86 (94%)	2%	20%	58%	14%
Lymphoedema massage	73 (90%)	48%	36%	5%	1%
Oedema massage	86 (95%)	25%	42%	20%	9%
Prescribed Homework: Scheduled as time contingent	85 (93%)	6%	22%	48%	16%
Prescribed Homework: Scheduled as pain contingent	85 (93%)	25%	36%	19%	14%
Sensory mapping training	70 (86%)	42%	32%	12%	1%
Discrimination training	74 (91%)	40%	28%	19%	5%
Desensitising training	76 (94%)	2%	20%	58%	14%
Graded Motor Imagery (GMI) in classic order	71 (90%)	43%	20%	15%	10%
GMI in your own order or ad hoc	73 (90%)	44%	27%	16%	2%
Mirror exercise	78 (96%)	21%	31%	35%	10%
Prism exercise	69 (85%)	78%	7%	0%	0%
Relaxation exercises	73 (90%)	11%	33%	33%	12%
Breathing control	75 (93%)	12%	33%	33%	14%
Cognitive techniques for pain control	73 (90%)	22%	33%	26%	9%
Problem solving techniques for pain control	74 (91%)	20%	31%	25%	16%
Cognitive Behavioural Therapy (CBT)	72 (89%)	48%	15%	22%	4%
Acceptance and Commitment Therapy (ACT)	68 (84%)	70%	9%	4%	1%
Transcutaneous Electrical Nerve Stimulation (TENS)	73 (90%)	21%	44%	23%	1%
Iontophoresis	71 (90%)	86%	0%	1%	0%
Soft tissue mobilisation	74 (91%)	9%	41%	37%	5%
Trigger point release	73 (90%)	11%	53%	26%	0%
Acupuncture	81 (100%)	81%	9%	11%	0%

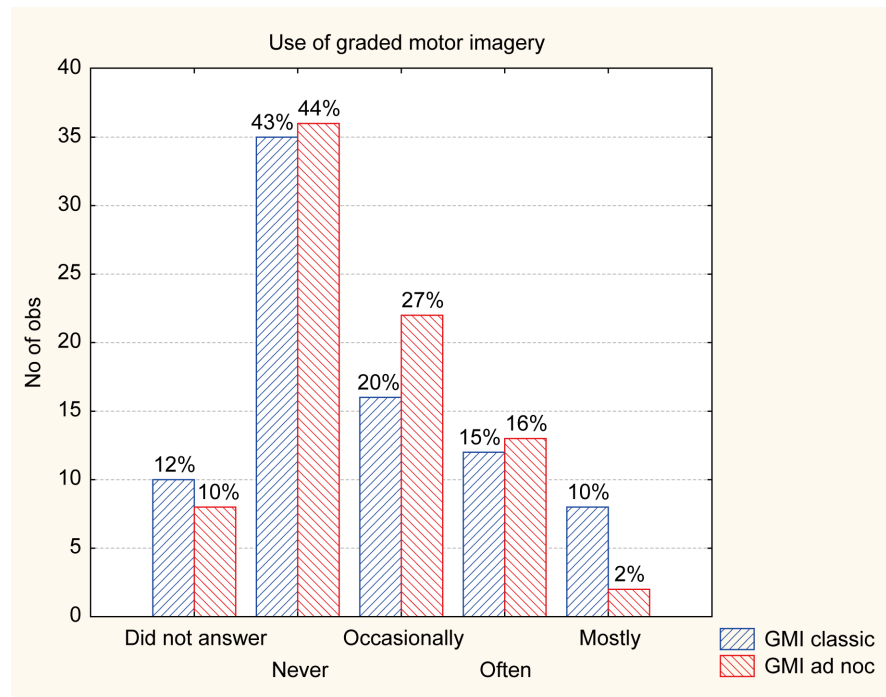


Figure 2. Use of graded motor imagery in clinical physiotherapy practice.

Table 2. Significant differences between those Physiotherapists who saw CRPS seldom versus those who saw CRPS patients often.

Physiotherapy intervention method more likely to be used by the physio who sees CRPS patients more often	Frequency of use more likely	P value
Graded Motor Imagery (GMI)	From occasional to often	0.017
Relaxation techniques	From occasional to often	0.021
Sensory-Motor training (SMT)		
• Sensory mapping	• From never to occasional	0.007
• Discrimination	• From never to occasional	0.007
• Desensitising	• From occasional to often	0.007
Oedema massage	From seldom to often	0.029

Beliefs about what was considered most effective for the management of CRPS patients proved highly variable. Physiotherapists were almost equally divided about whether or not reducing the pain experience was essential to improve the functioning (51% and 43%, respectively). This is shown in [Figure 3](#).

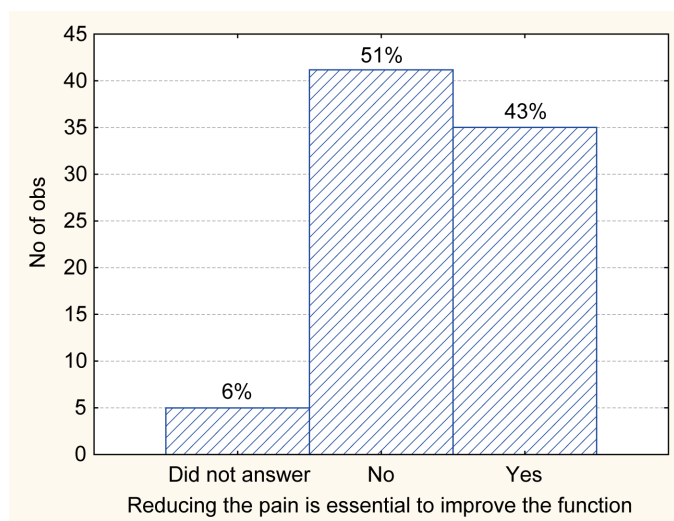
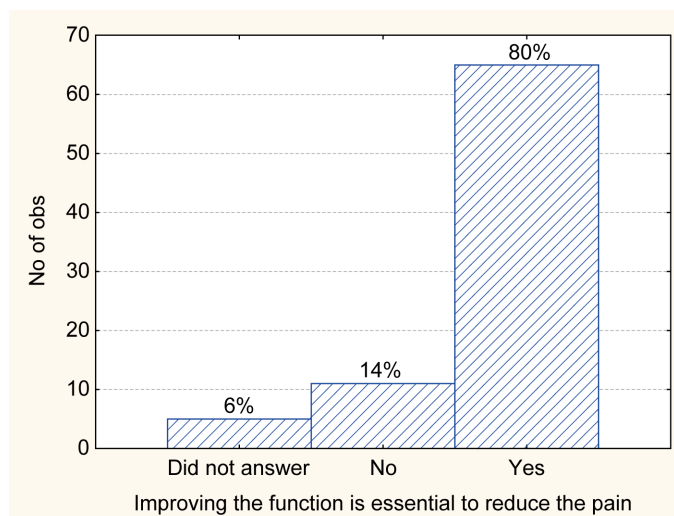
Eighty per cent believed that improving the function was essential to reduce pain; 14% believed that it was not essential. This is shown in [Figure 4](#).

Physiotherapists were equally divided on their beliefs about exercise and pain being either indicated or contraindicated in CRPS. These beliefs are shown in [Figure 5](#).

The beliefs were summarised and are represented in [Table 3](#).

Table 3. Summary of Physiotherapist beliefs about what is best for CRPS intervention method.

Physiotherapist beliefs about what is best for CRPS intervention method			
	Did not answer	Yes	No
	n (%)	n (%)	n (%)
Reducing the pain is essential to improve the function	5 (6%)	35 (43%)	41 (52%)
Improving the function is essential to reduce the pain	5 (6%)	65 (80%)	11 (14%)
Exercising and increasing the pain is contraindicated	6 (7%)	17 (21%)	58 (72%)
Exercising and increasing the pain is indicated	6 (7%)	14 (17%)	61 (75%)

**Figure 3.** The belief about reducing the pain being essential in CRPS to improve the functioning.**Figure 4.** Improving the function is essential in order to reduce the pain experience.

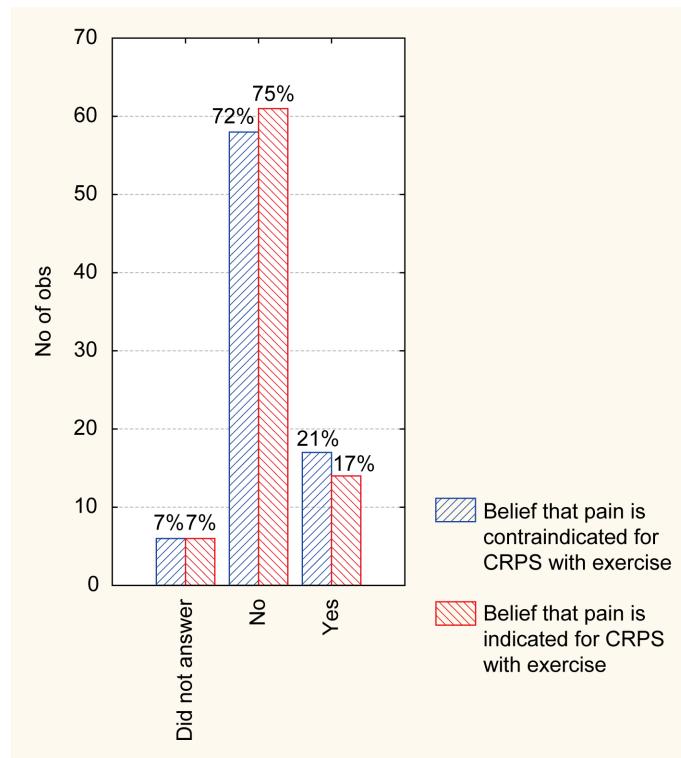


Figure 5. Beliefs about exercise and increasing pain being indicated or not for CRPS.

6. Discussion

These data provide the first contribution to literature about a systematic survey of physiotherapy and CRPS management in everyday clinical practice. Half of all New Zealand South Island physiotherapy practices do not manage CRPS patients. Only 10% of the Physiotherapists that manage CRPS patients treat more than two CRPS patients per month. Education was most often used as an intervention for CRPS. This was recorded by 83% of the Physiotherapists who together with Anaesthetists play an important role in education as CRPS patients possess a sub-minimum standard of basic knowledge about the syndrome [25]. Similar to diseases like diabetes, education enables behavioural change as well [26].

The data showed that the more frequently Physiotherapists evaluated CRPS patients, the more likely they were to use interventions with moderate based evidence, such as GMI and SMT. However, GMI and SMT were not used by many other Physiotherapists who evaluate CRPS patients less frequently. It is not possible to determine the reasons for these differences. This clearly needs further investigation. It has been suggested that physiotherapy management for CRPS needs to be specifically personalised [27]. This can be particularly difficult, as CRPS presentations, progression and outcome are variable. There is little specific evidence about what intervention to apply and when [28]?

These data illuminated the inconsistency with which physiotherapy interventions (other than education that is mostly used) are practised by those managing CRPS patients. A third of the sample often used cognitive techniques and

breathing control with relaxation techniques; another third used them occasionally. Those treating more CRPS patients are more likely to use the above technique rather than occasionally. Less than 15% are most likely to use these techniques. Eighty per cent are familiar with these interventions but do not apply them regularly.

Beliefs were divided about pain reduction being essential or not for improving the function of the affected CRPS limb. Eighty per cent believed that by improving function, the pain is reduced. Exercising and increasing the pain was a belief supported by 17%. It was found that 49% applied active exercises despite pain, but then only occasionally. When asked whether pain was contra-indicated or not for CRPS exercises, the groups were almost equally divided. Half believed that it was inevitable to have some pain with exercise; only 17% of this group believed that pain with exercise was really necessary.

Holding different beliefs influences the interventional modalities chosen for pain reduction or improvement in function for the treatment of CRPS patients. It influences the relationship the Physiotherapist has with the referring Anaesthetist. Applying any intervention by one half of Physiotherapists can become potentially difficult, if pain exacerbation is thought to be contraindicated, as pain forms the hallmark of CRPS. There are CRPS patients who present with reasonable function, but suffer severe pain [29]. The clinical presentation of CRPS remains inconsistent [1] [2] [30] [31] [32] [33]. Resolving how beliefs influence CRPS management is essential.

A weakness of the study is the relatively small sample size with potential bias being represented by the 57% response rate. Another weakness of the study is the use of Likert scale for measuring the frequency of the physiotherapy interventions that is not formally validated.

The strength is that this study provides the first evidence to represent data across a region, about Physiotherapist beliefs and usual interventions for CRPS patients. The use of self-reporting questionnaires as a valid measure is supported [34]. Future studies should be undertaken to develop validated questionnaires about beliefs around CRPS for Anaesthetists in Pain Management, Physiotherapists, and other health care providers, as well as for patients suffering from CRPS. It is important to determine how these beliefs influence referral, intervention method(s) and patient outcomes.

7. Conclusion

CRPS is not common on the South Island of New Zealand. Usual physiotherapy interventions vary widely. Different beliefs exist about the importance of managing the pain experience and the importance of improving function. These reflect the dichotomy seen in current evidence. Education is the most commonly used intervention. Those treating more CRPS patients are more likely to use interventions such as GMI and SMT often (rather than seldom, or not at all). How Anaesthetists in Pain Management and Physiotherapy beliefs about pain management and functional restoration affect CRPS outcomes requires closer scrutiny.

Conflict of Interest

The authors declare no conflict of interests regarding the publication of this paper. No funding contribution was received towards selection, extraction or analysis of the data from any source.

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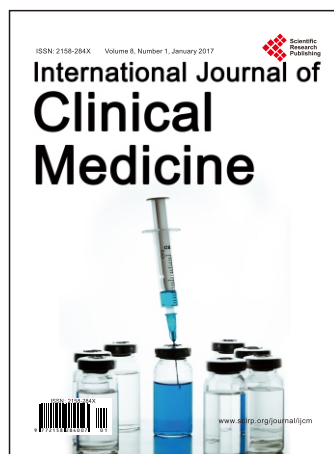
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International Journal of Clinical Medicine (IJCM) is a peer reviewed journal dedicated to the latest advancement of clinical medicine. The goal of this journal is to keep a record of the state-of-the-art research and to promote study, research and improvement within its various specialties.

Subject Coverage

The journal publishes original papers including but not limited to the following fields:

- Allergy and Clinical Immunology
- Cancer Research and Clinical Oncology
- Clinical Anaesthesiology
- Clinical Anatomy
- Clinical and Applied Thrombosis/Hemostasis
- Clinical and Experimental Allergy
- Clinical and Experimental Dermatology
- Clinical and Experimental Hypertension
- Clinical and Experimental Immunology
- Clinical and Experimental Medicine
- Clinical and Experimental Metastasis
- Clinical and Experimental Nephrology
- Clinical and Experimental Ophthalmology
- Clinical and Experimental Optometry
- Clinical and Experimental Otorhinolaryngology
- Clinical and Experimental Pathology
- Clinical and Experimental Pharmacology and Physiology
- Clinical and Molecular Allergy
- Clinical and Translational Oncology
- Clinical Anesthesia
- Clinical Apheresis
- Clinical Autonomic Research
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- Clinical Biomechanics
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- Clinical Neuropsychology
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- Controlled Clinical Trials
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- Innovations in Clinical Neuroscience
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- Neurophysiologie Clinique/Clinical Neurophysiology
- Nutrition in Clinical Practice
- Pacing and Clinical Electrophysiology
- Psychiatry in Clinical Practice
- Therapeutics and Clinical Risk Management
- Veterinary Clinical Pathology

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Notes for Intending Authors

All manuscripts submitted to IJCM must be previously unpublished and may not be considered for publication elsewhere at any time during IJCM's review period. Paper submission will be handled electronically through the website. All papers are refereed through a peer review process. Additionally, accepted ones will immediately appear online followed by printed in hard copy. For more details about the submissions, please access the website.

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