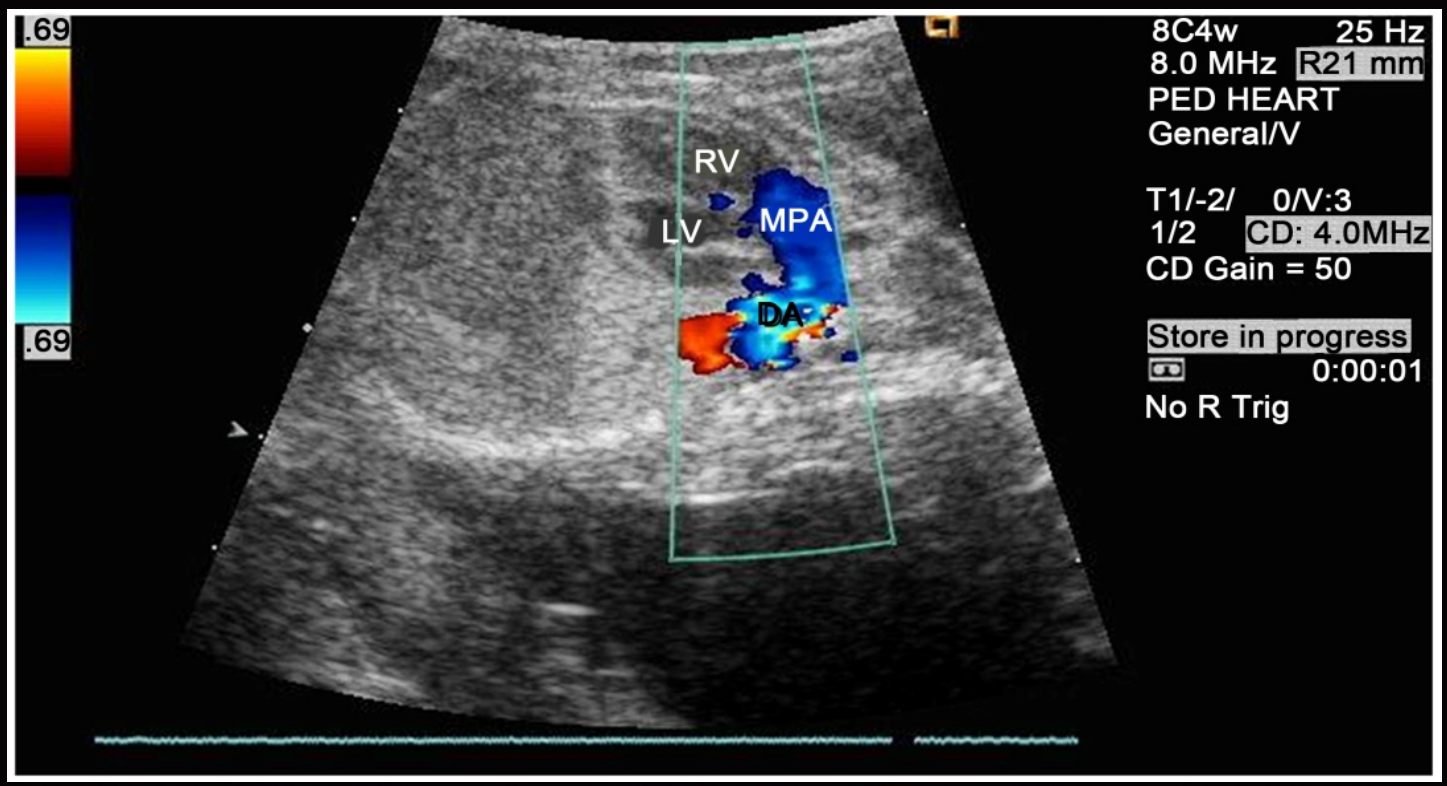
ISSN: 2158-284X Volume 7, Number 10, October 2016

Scientific Research Publishing

International Journal of Clinical Medicine



ISSN: 2158-284X
9 772158 284007 10

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ISSN: 2158-284X (Print) ISSN: 2158-2882 (Online)
http://www.scirp.org/journal/ijcm

Scientific Research Publishing

International Journal of Clinical Medicine, 2016, 7, 653-721
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

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Volume 7 Number 10 October 2016

The figure on the front cover is from the article published in International Journal of Clinical Medicine, 2016, Vol. 7, No. 10, pp. 685-689 by Brian Benjamin, Marcus Schamberger and Eric Ebenroth.

International Journal of Clinical Medicine (IJCM)
Journal Information

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Scientific Research Publishing

International Journal of Clinical Medicine, 2016, 7, 653-667
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Fasting for Laboratory Tests Poses a High Risk of Hypoglycemia in Patients with Diabetes: A Pilot Prevalence Study in Clinical Practice

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How to cite this paper: Aldasouqi, S., Corser, W., Abela, G.S., Mora, S., Shahar, K., Krishnan, P., Bhatti, F., Hsu, A. and Gruenebaum, D. (2016) Fasting for Laboratory Tests Poses a High Risk of Hypoglycemia in Patients with Diabetes: A Pilot Prevalence Study in Clinical Practice. *International Journal of Clinical Medicine*, **7**, 653-667.
http://dx.doi.org/10.4236/ijcm.2016.710071

Received: July 21, 2016
Accepted: October 17, 2016
Published: October 20, 2016

Abstract

Objective: Fasting for lipid profiles is a deeply-rooted tradition that is being revisited. In patients with diabetes, such fasting poses a risk of hypoglycemia, as observed in recent studies and case reports. This iatrogenic, overlooked, form of hypoglycemia has been referred to as Fasting-Evoked En-route Hypoglycemia in Diabetes (FEEHD). The objective of the study is to determine the prevalence of FEEHD in clinical practice. Methods: A two-page survey was administered to adults with diabetes on anti-diabetic medication(s). Patients were asked if they recalled having experienced hypoglycemia while fasting for laboratory tests (FEEHD) during the preceding 12 months. Results: Of 168 patients enrolled, 166 completed the survey, with a mean age of 55.3 (SD: 15.4) years. Seventy-nine (47.6%) were females. Of these 166 patients, 119 (71 %) had type 2 diabetes. Forty-five patients (27.1%) reported having experienced one or more FEEHD events. Notably, only 31.1% of the patients who experienced a FEEHD event informed their provider of the event, and only 40% of FEEHD events reportedly resulted in any subsequent provider-made medication change(s) to prevent future events. Conclusions: This is the first study of FEEHD prevalence in clinical practice, the results of which serve to increase awareness amongst

clinicians about the occurrence of FEEHD. We believe that FEEHD appears to be overlooked by clinicians. The prevalence of FEEHD in clinical practice is strikingly high (27.1%). More concerning is the significant underreporting of FEEHD events by patients to their clinicians (31%). We hope this study will trigger further investigation to confirm these preliminary findings and modify practice guidelines.

Keywords

Fasting, Lipids, Glucose, Hypoglycemia, Lipid Profiles, Nonfasting, FEEHD

1. Introduction

Lipid profiles are conceivably the most commonly used laboratory tests that traditionally require overnight fasting. Since patients with diabetes, especially type 2 diabetes mellitus (T2DM), have a high prevalence of lipid abnormalities [1], these patients expectedly undergo frequent lipid testing. Conceivably not originally based on compelling evidence, the current, deeply-rooted, practice of fasting for lipid profiles as recommended by current guidelines [2], has been recently challenged [3]-[9]. As important, there is an emerging discussion about the atherogenicity of postprandial hypertriglyceridemia, which can be missed in fasting lipid profiles [5]-[13].

In addition to the inconvenience and questionable necessity of fasting for lipid profiles in clinical practice, there is ongoing discussion regarding the safety of such fasting in patients with diabetes [7] [9]-[13]. As recently reported, patients with diabetes on hypoglycemic medications are especially vulnerable to fasting that can increase their risk for hypoglycemia especially if they are not adequately prepared for fasting [10]-[12]. Specifically, patients with diabetes who use insulin or sulfonylureas are put at increased risk for hypoglycemia when fasting [10]-[13]. Whereas patients who are not taking hypoglycemic medications (*i.e.*, insulin and insulin secretagogues) are protected by a complex physiological response that inhibits insulin production by the beta cells during fasting, patients taking such medications typically do not have such a protective mechanism in view of continued circulating insulin [10]. This risk is further aggravated in patients with long-standing diabetes due to the loss of additional counter-regulatory mechanisms that protect from hypoglycemia during fasting, *i.e.*, glucagon and catecholamines [12]-[15].

We recently described a "novel" form of hypoglycemia referred to as Fasting-Evoked En-route Hypoglycemia in Diabetes or FEEHD [9] [11]-[13]. FEEHD as defined herein is diagnosed by the following criteria: Documented hypoglycemic event (blood glucose below 70 mg/dL) in patients with diabetes who take insulin or sulfonylurea, or both, who fast overnight for lab tests (and thus miss or delay breakfast), and who commute to the laboratory facility while fasting. The condition in a broader term can be applied to any fasting-related hypoglycemic event in patients with diabetes who are taking hypoglycemic medications (e.g., occurring at home or elsewhere). We restricted the definition in the acronym to reflect this "en-route" circumstance. This terminology, thus, high-

lights the risk of this form of hypoglycemia that can potentially occur during driving to and from the laboratory for blood testing. This poses a significant threat given that hypoglycemia during driving has been shown to impair performance and lead to traffic accidents [16].

To our knowledge, the morbidity or mortality associated with FEEHD has not been studied, and we believe that this might be due to under recognition and under reporting [9]-[13]. However, upon more meticulous literature search, we came across one case report of laboratory-associated hypoglycemia from Thailand, which reported on a patient who died in the laboratory waiting room, while waiting for a fasting lab test [17]. She was reportedly on sulfonylurea and her blood glucose was reported as 0 (zero) mg/dL. Unlike FEEHD, however, diabetes-associated hypoglycemia and associated morbidity and mortality have been well-studied as being the "major limiting factor in diabetes management" [14] [15].

While FEEHD has been described recently in two small studies [10] [11] and a case series [12], the exact prevalence of FEEHD remains largely unknown. Thus, we hypothesized that this form of iatrogenic hypoglycemia is widely prevalent in clinical practice but judging from the dearth of reports is greatly under recognized. In this pilot study, we set out to evaluate the prevalence of FEEHD in a real life clinical setting.

2. Materials and Methods

This study was approved by Michigan State University's (MSU) and Sparrow Hospital's Institutional Review Boards. Informed consent was obtained from all participating patients. Patients were recruited from multiple clinics, as detailed below.

2.1. Selection of Patients

The study was conducted at four clinical sites: three MSU and Sparrow Hospital teaching clinics: Internal Medicine, Family Medicine and Endocrinology (Diabetes) clinics, in East Lansing and Lansing, Michigan, and The Care Free Clinic, a non-for-profit family medicine clinic for the underserved in Lansing, Michigan. The selection of the aforementioned clinics was made at random: Those were the fairly diverse set of clinics that data collectors (residents or students) happened to have access to at the time.

Inclusion criteria included adult patients who: were able to understand and answer the survey questions; had a confirmed diabetes diagnosis; and who were taking insulin and/or oral hypoglycemic agents (OHA's) or non-insulin injectable medications. Exclusion criteria included: patients who were unable to understand or complete the survey questionnaire even with assistance; patients who were not taking medications regularly; and surveys that were not completely filled.

2.2. Study Design

The study was conducted from October 2014 to October 2015. The research protocol consisted of a two-page written survey that was offered to patients attending the participating clinic sites. Patient inclusion and exclusion criteria were determined by data

collectors: attendings, fellows, residents, medical students or by research-dedicated medical assistants (MA) in the clinics. Once a potentially eligible patient was identified, the MA would either complete the study enrollment using a pre-signed survey or would ask a non-MA data collector to enroll the patient.

If a participant expressed reluctance to complete the survey because of time constraints, he or she was given the option to complete the questionnaire at home and mail it to the clinic.

2.3. Survey Questionnaire

The survey questionnaire was designed by the study investigators. It is a simple, customized survey tool that was adapted from original questionnaires used in prior studies [10] [11], which were preliminary questionnaires intended strictly to help obtain raw information from patients to collect data in a structured manner about hypoglycemic events and circumstances thereof. The questionnaire had not been validated in prior studies, and was not intended for sophisticated larger-sample statistical analysis. Thus, the reliability of the questionnaires was not validated but was utilized in this pilot study as a facilitator in data collection.

The customized questionnaire used in this study (shown in Appendix)is a two-page simple-language survey which included, in addition to demographics and clinical info, specific questions about the number of fasting lab tests, the number of hypoglycemic events in general and the number and circumstances of FEEHD events. Hypoglycemia in patients with FEEHD was defined similar to the definition of diabetes-associated hypoglycemia in general, that is blood glucose below 70 mg/dL, as defined in the literature [15]. All specific questions about hypoglycemic events were limited to the preceding 12 months. At the end of the survey, a template notification was made to instruct patients to notify their care providers of any hypoglycemic events to implement preventive measures.

2.4. Statistical Analysis

For this pilot study, the investigators had opted to avoid trying to conduct any pre-hoc minimal sample size calculations due to the largely unknown characteristics of the anticipated patient samples across the clinic settings. Survey questionnaires were then reviewed and entered into Excel spreadsheets and a series of cross tabulations were generated to examine for statistically significant sample subgroup differences. During Chi-square calculation and analysis of variance (ANOVA), procedures were completed with complete data sets. Variables tested to evaluate correlations with patient characteristics and the occurrence of FEEHD episode(s) included: a) clinic type (*i.e.*, Diabetes versus other primary care clinics); b) sex; c) total number of FEEHD-associated medications taken during year; d) type of diabetes; e) duration of diabetes; f) number of reported all-cause hypoglycemic episodes during the prior year; and g) total number of fasting lab orders issued during the prior year. Finally, a series of conservative forward stepwise binary logistic regression procedures free of parametric assumptions were

completed to examine for categorical factors and continuous covariates that were significantly associated with the occurrence of hypoglycemic episodes(s).

3. Results

One hundred sixty-eight patients consented to participate in the study, of whom 166 patients completed the surveys in the clinic, and 2 patients took the survey to be completed at home. After the exclusion of 2 patients who did not complete the study surveys, a final sample of 166 respondents was achieved. The mean age of patients was 55.3 years (SD 15.4), and diabetes duration averaged 16.7 years (SD 12.3). A total of 79 (47.6%) patients were females, and 119 (71.7%) reported having been diagnosed with T2DM (Table 1).

In regards to current medication regimen, 24 (14.7%) reported taking one or more OHA's only; 58 (34.9%) reported taking insulin or other injectable medications with no OHA's; and 83 (50.0%) patients reported taking both types of medications. Patients indicated having received a mean of 2.4 (SD 21.7) fasting lab orders during the past 12 months. A total of 103 (62%) of patients reported having experienced between one and four all-cause hypoglycemic episodes during the past year.

Table 1. Descriptive characteristics of patients and results of key questions in the study's survey questionnaire.

Age, mean (SD)	55.3 (15.4)
Sex, male (%)	87 (52)
Type 2 diabetes (%)	119 (71)
Duration of diabetes, mean (SD)	16.7 (12.3)
Number of fasting labs reported during prior year, mean (SD)	2.45 (2.17)
Question: "Did you experience one or more reported lab-related FEEHD episode during prior 12 months?" (%)	45 (27.1)
"Could you recall circumstance(s) related to FEEHD episode?"	39 (87)
"Do you remember clearly advising provider of FEEHD episode?"	14 (31)
"Did your FEEHD episode result in medication change?"	18 (40)
Question: "How many hypoglycemic episodes of all causes have you experienced during prior 12 months?" mean (SD)	1.52 (1.60)
Total number of current diabetes medications (%)	
OHAs only	24 (15)
Insulin(s) only	58 (35)
Both OHAs and insulin(s)	83 (50)
Number of reported FEEHD-associated medications during prior year. mean (SD)	1.72 (0.86)

Abbreviations: SD = standard deviation; FEEHD = fasting-evoked en-route hypoglycemia in diabetes; OHAs = oral hypoglycemic agents.

Of the 166 sample patients, 45 (27.1%) patients reported having one or more lab-related FEEHD hypoglycemic events during the past 12 months. Within this sample subgroup, 39 (86.7%) patients could recall at least one specific circumstance related to their FEEHD episode(s). These included (frequently overlapping) reasons such as: 1) fasting/eating less during prior night (33%); 2) exercising (4%); 3) recent medication changes (3%); and 4) multiple cited reasons (19%). Notably, only 31.1% of patients who experienced FEEHD clearly indicated that they had advised their providers of the event. Of concern as well, only 40% of FEEHD events reportedly resulted in any subsequent provider medication change(s).

Major non-significant correlations with patient characteristics and FEEHD episode(s) during prior 12 months included 1) clinic type (Pearson r = −0.069, $p = 0.378$); 2) gender (r = 0.012, $p = 0.882$); 3) total number of FEEHD-associated medications taken (r = 0.083, $p = 0.292$); and (4) total number of fasting lab orders received during prior year (r = 0.000, $p = 0.999$). On the other hand, patient characteristics that were significantly correlated with experiencing one or more FEEHD episode during the prior 12 months included: 1) type of diabetes (r = −0.175, $p = 0.026$); 2) duration of diabetes (r = 0.173, $p = 0.042$); and 3) number of reported all-cause hypoglycemic episodes during the prior 12 months (r = 0.305, $p =< 0.001$). In summary, T2DM; diabetes duration for 11 or more years; and/or multiple all-cause hypoglycemic episodes were more likely correlated with experiencing one or more FEEHD episode(s) during the prior 12 months.

Furthermore, variables such as age category ($p = 0.758$), gender ($p = 0.568$), clinic type ($p = 0.685$), number of prior annual fasting labs during prior 12 months ($p = 0.761$), and total number of FEEHD-associated medication(s) taken during prior year ($p = 0.779$), each with score test statistics of $p > 0.10$ were removed from later models. In the final logistic regression model, only one covariate demonstrated statistical significance: The frequency of all-cause hypoglycemic episodes during prior 12 months ($p = 0.014$). Of note, patients' categorical diabetes duration just barely fell out of statistical significance ($p = 0.054$). **Table 2** summarizes the variables as predictors of FEEHD events.

Finally, the study was not designed to evaluate for possible association of FEEHD with factors that could influence the risk of hypoglycemia, including medications types or doses; comorbidities such as liver or kidney disease; the duration of the fasting; etc. The whole mark of the study design was the fasting itself (and skipping a meal), being iatrogenic and a known major cause of hypoglycemia in patients on hypoglycemic medications (insulin and sulphonylureas).

4. Discussion

This study supports the hypothesis that FEEHD occurs in clinical settings with a surprisingly high prevalence (27.1%). To our knowledge, this is the first study to evaluate the prevalence of FEEHD in clinical practice. In our previous studies [10] [11], study designs did not allow for prevalence calculation. While we cannot necessarily extrapolate

Table 2. Predictors of FEEHD event(s) during 12-month pre-survey period* (N = 166 adult patients).

Factor	Wald	Exp (B)	95% CI	*p* Value
Age (Reference group 64 - 89 years)**				0.758
19 to 50 years				0.556
51 to 60 years				0.976
Sex (Reference group females)**				0.568
Clinic type (Reference group diabetes clinic)**				0.685
Internal medicine clinic				0.424
Family medicine #1 clinic				0.296
Family medicine #2 clinic				0.587
Type of diabetes: (reference group Type 1)**				0.343
Number of annual pre-survey fasting labs***				0.716
Total number of FEEHD-associated medications taken during prior year***				0.779
Diabetes duration in years (Reference group "greater than 20 years")**	5.824			0.054
1-10 Years	2.498	0.402	0.130 - 1.245	0.114
11-20 Years	0.839	1.581	0.593 - 4.214	0.048
All-cause frequency of hypoglycemic episodes during prior 12 months***	6.053	1.462	1.080 - 1.978	0.014*

Abbreviations: FEEHD = fasting-evoked en-route hypoglycemia in diabetes; Exp (B) = the Exp (B) is equivalent to the "Odds Ratio" with numbers less than 0.500 representing less than 50% likelihood of a FEEHD occurring (e.g. the 0.402 for patients with diabetes duration of 1 - 11 years) versus more likely (e.g. patients with 11 - 20 years of diabetes (1.581)—about one and a half more likely) of experiencing one or more FEEHD event(s). In other words, patients with longer history of diabetes were generally more likely to experience a FEEHD event, although not quite significantly ($p = 0.054$). *Patients may have experienced mare than one FEEHD event during 12-month study window; **Categorical variable; ***Continuous variable.

these findings to other clinical settings, we believe that FEEHD is likely to be quite highly prevalent in clinical practice, but is perhaps under recognized. Considering 70 mg/dL as the cut off for diabetes-associated hypoglycemia [15], the severity of hypoglycemia reported by patients who recalled the exact glucose measurement ranged from 30 to 69 mg/dL. Of concern, 10 patients reported FEEHD events below 50 mg/dL and five patients reported events below 40 mg/dL, with variable reported hypoglycemic symptomatology.

FEEHD is a recently recognized circumstantial category of hypoglycemia [7] [9]-[13] that is largely preventable. More concerning is that it is primarily iatrogenic. Hypoglycemia, described by Fowleras being "in many ways the Achilles heel of diabetes treatment", is the major limiting factor in diabetes management [14], with significant morbidity and mortality [15]. It is conceivable that diabetes-related hypoglycemia is a heterogeneous, multifactorial and complex condition. Multiple factors interplay to precipitate hypoglycemia in patients with diabetes, such as carbohydrate intake, medications,

physical activity and comorbid conditions—but the common denominator is a net imbalance between medications (mainly insulin or sulfonylureas) and carbohydrate intake. The American Diabetes Association's (ADA's) practice guidelines emphasize the importance of teaching patients to balance insulin use, carbohydrate intake and exercise, adding that these strategies are not always sufficient to prevent hypoglycemia [1].

FEEHD is such a circumstance of a skipped meal that is imposed on patients by their caregiver; ordering fasting labs in patients with diabetes, without educating them to adjust their anti-diabetic medications, and to perform more glucose monitoring while fasting. More concerning, our study demonstrated that less than one-third of patients informed their clinicians about the occurrence of FEEHD and only 40% of patients had implemented strategies to prevent future FEEHD episodes. Although this iatrogenic form of hypoglycemia has been reported since 2011, currently there are no guidelines related to FEEHD [7] [9]-[13]. However, to increase awareness about FEEHD, the results of the published studies were communicated to the ADA via the online portal for public proposals suggesting the education of patients about FEEHD in the practice guidelines. As a result, in 2012 the ADA provided [18] an addendum to the thereto guidelines (2011) in the "Hypoglycemia" section [19], to include the following statement: *"*Patients should understand situations that increase their risk of hypoglycemia, such as fasting for tests*"* [18].

However, this statement would need to be implemented with various educational routes to clinical practice. Moreover, current investigators have now implemented a preventive program [11] in their clinic (attempting to streamline the fasting pre-requisite for lipid profiles, the principal lab test requiring fasting). The preventive program also implemented educational instructions for patients who are; nevertheless, requested to fast for any labs, explicitly describing medication changes and frequent glucose monitoring [11].

We had conducted a previous study after implementing the above preventive program and did a retrospective design comparing two groups of patients, one with the teaching intervention and one without. The study demonstrated a significant reduction of FEEHD in the group that received instruction prior to fasting for blood testing. Hypoglycemia was reduced by over 50% in the glucose levels of 70 mg/dL, 88% for 50 mg/dL and 100% below 40 mg/dL [11].

Two major concerns regarding FEEHD need to be emphasized:

- Many patients do not have a clear understanding of hypoglycemia, and physicians do not seem to track the frequency of hypoglycemia in their patients. Thus hypoglycemia is conceivably underreported, as emphasized by Moghissi [20] and by Skarulis and Hirshberg [21] that hypoglycemic events are often underreported by patients to their clinicians.
- Diabetes-associated hypoglycemia occurring during driving has been reported to occur in 19% of T2DM in a national survey report [20]. A growing concern is emerging in regards to hypoglycemia and driving [14] [22]-[25]. The ADA's practice guidelines emphasized that "severe hypoglycemia can cause acute harm to the per-

son with diabetes or others" [1]. Also, there is an emerging concern of litigation regarding hypoglycemia and traffic accidents [25]. Currently, we are not aware of reported cases for FEEHD occurring while driving, but there is a potential risk of this occurrence, and there is a concern of underreporting of such cases.

In parallel to this discussion, it is prudent to emphasize that in clinical practice lipid profiles are the commonest lab tests requiring fasting, including in patients with diabetes. Coincidentally, recent compelling literature has cast a doubt on the necessity of fasting for lipid profiles, altogether [3]-[13] [26]-[33] which is a stark departure from a decades-long tradition. But still, most national and international guidelines continue to recommend fasting for lipid profiles [2] [30]-[33]. This is despite the compelling evidence that fasting is not only unnecessary for lipid profiles [6] [8] [30]-[33], but in addition studies have shown that non-fasting lipid profiles are probably more relevant as predictors of cardiovascular disease [8] [26] [27]. Numerous studies have found that nonfasting lipids are not inferior to fasting, as cardiovascular disease predictors [32].

Interestingly, this deeply-rooted tradition of fasting for lipid profiles is slowly changing, however. In the US, most organizations continue to recommend fasting for lipid profiles for initial evaluation and monitoring of lipid status. However, over the last decade guidelines have evolved with more guidelines recommending that non-fasting measurement of total and high-density lipoprotein (HDL) cholesterol could be alternatively utilized, the so-called Non-HDL cholesterol [32]. Furthermore, the American Heart Association in its 2013 guidelines [32] emphasized that while the guidelines prefer fasting but fasting is not considered mandatory, nevertheless [32]. As a recent departure from the tradition of routine fasting, a recent Veterans Affairs' guideline explicitly recommended against fasting for lipid tests, except when triglycerides exceed 400 mg/dL [28]. Similarly, The Danish National Society of Clinical Biochemistry's Guidelines, now recommends non-fasting lipid profiles, with "the possibility of" ordering a fasting test if the nonfasting triglycerides level is over 350 mg/dL [29], More explicitly, Langsted and Nordestgaard (lipid experts from Denmark) recently published an editorial in the journal, *Chemical Chemistry*, in which they stated that "nonfasting lipid profiles are the way of the future" [30].

An entertaining example of how this issue is still being debated, at present, can be seen in a Q&A article recently published in the journal of Clinical Chemistry [31], in which six international lipid experts were interviewed. The experts were each asked a set of questions about the issue of fasting versus nonfasting lipid testing. On the final question "*Do you personally believe that nonfasting samples should be used for routine lipid profiles*?", four experts said "yes" and two said "no", with diverse elaborations!

Most recently, the most powerful step towards the push for nonfasting lipid profiles, so far, has been taken by an international expert panel (21 experts including 3 from the US) convened by the European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine, which developed a joint consensus statement, simultaneously published ahead of print in two major medical journals [33]. The consensus statement, stated that "Fasting is not routinely required for determination of

a lipid profile", and proposed cut-point values for nonfasting lipid components to be flagged by laboratories.

The primary limitations of this study include a sample size that is small; lack of exact calculation of survey response rate; data that is acquired based on patients' recollection of the hypoglycemic events and glucose measures; a survey questionnaire that did not include the type of tests for which fasting was requested. Finally, the study did not address if patients were driving themselves to and from the laboratory nor if FEEHD events caused traffic accidents. However, despite these limitations, this pilot study can serve as an initial step in bringing attention to this serious and often overlooked management problem in patients with diabetes. We suggest larger population-based studies be performed to evaluate the prevalence of FEEHD.

5. Conclusion

This is the first prevalence study to evaluate the prevalence of FEEHD in clinical practice. The high prevalence (27.1%) noted in this study is quite alarming, and as alarming is the apparent unawareness of this iatrogenic problem amongst clinicians. Although this is a pilot, non-randomized study, and despite the study's limitations, it is hoped that this pilot study triggers further studies of larger samples and improved designs to address the prevalence of FEEHD in other clinical settings and in the population. Finally, it is hoped that health organizations, especially diabetes organizations, take a note of this issue and develop specific educational guidelines to prevent FEEHD.

Acknowledgements

The authors would like to thank Ms. Jinie Shirey (Department of Medicine, MSU College of Human Medicine, East Lansing, MI) for assistance with manuscript preparation; Dr. Christie Clipper (Healthy Edge, Ann Arbor, MI) for revision of the manuscript; and senior librarians Laura Smith, Michael Simmons and Steve Kalis (Sparrow Hospital, Lansing, MI) for assistance with literature search. The authors also would like to thank the clinical and support staff at all clinical sites for facilitation of the study conduction, and finally to thank all patients who participated in the study.

The study was presented in part (as interim analysis) at the 2015 annual meeting of the American Association of Clinical Endocrinologists (AACE) in Nashville, TN and the 2015 annual meeting of the American College of Physicians Michigan Chapter in Traverse City, MI. Upon study completion, a final abstract of the study was presented at the 2016 annual meeting of AACE in Orlando, FL, May 24-29, 2016. The abstract was selected by AACE to be presented as an oral presentation, as a CME activity.

Author Disclosure Statement

SA: Speaker for Janssen Pharmaceutical and Sanofi Pharmaceutical.
GA: Speaker for Merck, Amgen and Diiachi Sankyo. He served as a consultant to Kowa Pharmaceutical. He was a participant at Merck's US Thrombosis Advisory Board and Atherosclerosis Global Therapeutic Experts Forum and he has received grant support

from Merck.

SM: Research support from Atherotech Diagnostics and NHLBI. She served as a consultant to Amgen, Quest Diagnostics, Lilly, Pfizer, and Cerenis Therapeutics.

Other co-authors: No conflict of interests.

Funding

None.

Authors Contributions

SA: Designed study; wrote/revised manuscript.

WC: Participated in study design; analyzed data; reviewed manuscript.

GA: Contributed to discussions; revised manuscript.

SM: Contributed to discussions; revised manuscript.

KS: Collected data; reviewed manuscript.

PK: Collected data; reviewed manuscript.

FB: Participated in study design; collected data; reviewed manuscript.

AH: Participated in study design; collected data; reviewed manuscript.

DG: Participated in study design; reviewed manuscript.

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Appendix

IRB-approved Survey Questionnaire, Page 1:

Fasting-Evoked En-Route Hypoglycemia in Diabetes (FEEHD)

Patient Name: Sex: M F Tel:

Date of Birth: / /19 Age: years

Diabetes: Yes No (If no then stop, you are done)

If yes: Type 1 Type 2 Other Duration: years

In the past 1 year, have you had a hypoglycemic (blood sugar less than 70) event while fasting for a laboratory blood draw? (Such as a cholesterol test)

Yes No

Do you remember how low your sugar was? If yes, what was it:

Medications at the time of the hypoglycemic event:

Insulin Pump Insulin Injections Diabetic Tablets (Orals/OHAs)

Insulin: Lantus Levemir Novolog Humalog Apidra

NPH 50/50 70/30 75/25 Regular Byetta

Bydureon Victoza Symlin

OHAs: Glipizide(Glucotrol) Glyburide(Diabeta) Glimeperide(Amaryl) pioglitazone(Actos) rosiglitazone(Avandia) Nateglinide(Starlix) repaglinide(Prandin) colesevelam(Welchol) Sitagliptin(Januvia) linagliptin(Tradjenta) alogliptin(Nesina) saxagliptin(Onglyza) Metformin(Glucophage/Fortamet/Glumetza) dapagliflozin(Farxiga) canagliflozin(Invokana) miglitol(Glyset) acarbose(Precose) Other:

Do you recall what your sugar was the night before, and the morning of the test? If yes, approximately what range:

Low High Average

Did you make changes on your diabetic medications the night before, or the morning of the test? If yes, what changes, and were they suggested by your physician:

Did you feel the low sugar? If so, what did you feel, and what did you do:

IRB-approved Survey Questionnaire, Page 2:

In the past 1 year, have you had other hypoglycemic (blood sugar less than 70) events at all? If so, how frequently?

Never Once Several Times Monthly Weekly Near Daily

What were the circumstances of the hypoglycemic event/s?

Fasting Forgot to eat Ate less than expected Post exercise

Recent medication changes (within the past week) Other:

Did you make your provider aware of your hypoglycemic episode/s? If yes, was your diabetic medications regimen changed, and if so how:

If your diabetic regimen has been changed after hypoglycemic episode/s, how has this changed the frequency of your hypoglycemic episodes:

No change Less frequent, if so how much: More frequent, if so how much:

Never Once Several Times Monthly Weekly Near Daily

To the best of your knowledge, how many times have you had fasting labs drawn in the past year?

How many times have the results of these labs resulted in changes to your therapy (medical regimen)?

Thank you for helping us to better understand, hypoglycemic events in diabetic patients, and what we may be able to do to minimize them!

Please notify your primary doctor or diabetes specialist if you have experienced any low sugars that they are not aware of, so changes in diabetes management can be made to avoid low sugars.

International Journal of Clinical Medicine, 2016, 7, 668-674
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Defining the Cause of Post-Operative Hyponatremia in the Orthopedic Patient

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How to cite this paper: Hennrikus, E., Georgeson, A., Leymeister, K., Mucha, S., McGillen, B. and Miller, R. (2016) Defining the Cause of Post-Operative Hyponatremia in the Orthopedic Patient. *International Journal of Clinical Medicine*, **7**, 668-674.
http://dx.doi.org/10.4236/ijcm.2016.710072

Received: August 11, 2016
Accepted: October 18, 2016
Published: October 21, 2016

Abstract

Background: Post-operative hyponatremia occurs after 30% of orthopedic surgeries, increasing morbidity, mortality and hospital length of stays and hospital costs. The cause of the hyponatremia can be varied, hard to diagnose and impact management. The goal of this study was to determine the causes of post-operative orthopedic hyponatremia and to evaluate the accuracy with which nephrologists and internists interpret the data. Methods: This was a retrospective chart review of patients >21 years old on the adult total joint service who developed postoperative hyponatremia. A hyponatremic order set was developed and patient fluid status was charted by the presence or absence of edema in non-surgical extremities. The patients were treated by their managing physicians. After one year, data on 51 patients were assembled and sent to three nephrologists and three internists to analyze and diagnose the etiology of the hyponatremia. Results: The most common causes of post-operative hyponatremia were hypovolemia (33.7%), the syndrome of inappropriate antidiuretic hormone, SIADH (32.4%), hypotonic fluid (8.2%), acute kidney injury (5.2%) and medications (5.9%). The interrater agreement, measured by kappa coefficient, was moderate (0.43; 95% CI 0.34, 0.53) for the nephrologists and fair (0.38; 95% CI 0.30, 0.46) for the internists. Conclusions: The majority of post-operative hyponatremia following total joint surgery in adults is from hypovolemia and SIADH. The treatment for these is very different: the first requires fluid resuscitation and the latter, free water restriction. Due to an interplay of peri-operative factors, the diagnosis can be difficult for both internists as well as nephrologists.

Keywords

Hyponatremia, Internists, Nephrologists, Hypovolemia, SIADH

1. Introduction

In a prior study, we found in our institution a 30% prevalence of post-operative orthopedic hyponatremia. Post-operative hyponatremia in the orthopedic patient is associated with longer hospitalizations, greater hospital costs, more frequent discharges to extended-care facilities [1] and higher mortality [2]. Identifying the cause and providing appropriate treatment can mitigate the adverse effects of hyponatremia [2]. Hypotonic fluid resuscitation, hypovolemia, medications, comorbidities and acute kidney injury can all cause hyponatremia in the post-operative state. Surgery can also produce non-osmotic stimuli for arginine vasopressin (AVP) release, resulting in the syndrome of inappropriate antidiuretic hormone (SIADH) [3]. Depending on the underlying cause, the treatment of hyponatremia can be markedly different.

However, due to the simultaneous interplay of multiple post-operative factors, diagnosing the cause of hyponatremia can be difficult [4]. In this study, three nephrologists and three internists individually diagnosed the cause of hyponatremia by retrospectively evaluating patient data obtained from a standard hyponatremia algorithm. Frequency of hyponatremia etiologic diagnoses and physician interrater agreement were then assessed.

2. Methods

2.1. Setting and Participants

A hyponatremia order set was developed for the hospital electronic medical record (EMR). After receiving IRB approval, the adult total joint orthopedic physician assistant was instructed to use this order set on all patients who developed hyponatremia post-operatively. He was also instructed to document in the EMR if the patient had edema of a non-operative lower extremity. The results of these findings were used at the discretion of the medical teams caring for the patients.

Inclusion criteria included: patient $\geq$ 21 years old, hospital admission to the total joint surgical service, normonatremia (serum sodium (Na) $\geq$ 135) at presentation and hyponatremia (serum Na < 135) [5] post-operatively. Na level was corrected for hyperglycemia using the formula: measured Na + 2.4 × (glucose mg/dL – 100)/100.

Demographic, lab, medication, comorbidity and clinical data were compiled for each patient. A de-identified spreadsheet was sent to three nephrologists and three internists to review. Each physician used the data to determine the etiology of each patient's hyponatremia.

2.2. Data Collection

Demographics: age, gender, type of surgery, preoperative (pre-op) date, surgical date and postoperative (post-op) day of first hyponatremia.

Physical exam:

Pre-op and post-op: blood pressure and pulse,

Post-op edema in a non-operative lower extremity.

Laboratory:

Pre-op: Serum: sodium (Na), potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine (Cr), glomerular filtration rate (GFR), glucose, hemoglobin (Hgb), hematocrit (Hct).

Post-op: Serum: Na, potassium, chloride, bicarbonate, BUN, Cr, GFR, glucose, osmolality, uric acid, Hgb, Hct.

Urine: Na, Cr, urea, osmolality.

Calculated: fractional excretion of Na (FeNa) and fractional excretion of urea (FeUr).

At the discretion of the managing physicians: thyroid stimulating hormone, cortisol.

Medications: thiazides, selective serotonin reuptake inhibitors (SSRI), nonsteroidal anti-inflammatory drugs (NSAID), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB).

Co-morbidities: hypertension, atrial fibrillation, coronary artery disease, congestive heart failure, cirrhosis, renal failure, hypothyroidism, diabetes, adrenal insufficiency.

2.3. Outcomes

The primary outcome was the percentage of total diagnosed etiologies for post-operative hyponatremia. The secondary outcome was the diagnostic overall agreement and interrater agreement between the three nephrologists and the three internists.

2.4. Analysis

All variables were summarized prior to analysis using frequencies and percentages or means, medians, and standard deviations. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). The mean change from pre-op to post-op in sodium, hemoglobin and hematocrit was tested using a paired t-test.

The prevalence of the etiologies of hyponatremia was determined by calculating the percent each diagnosis was named by all six evaluators.

The overall agreement of the six evaluators, the three nephrologists and three internists and the interrater agreement between each pair of evaluators were assessed using the weighted Cohen's kappa coefficient.

3. Results

Over the course of twelve months, fifty-one patients on the total joint service developed post-operative hyponatremia. A summary of the patients' demographic and clinical characteristics are outlined in Table 1.

Serum Changes

The patients had a statistically significant decrease in serum sodium from the pre-operative serum sodium levels (138.5 ± 3.3) compared to the post-operative sodium (131.1 ± 2.3, $P < 0.001$). Seventy-eight percent of hyponatremia occurred within one day after surgery. Hemoglobin (12.7 ± 2.3 vs. 9.5 ± 1.8, $P < 0.001$) and hematocrit (38.1 ± 6.1 vs. 28.6 ± 5.1, $P < 0.001$) decreased significantly postoperatively.

Etiology: Figure 1

Hypovolemia 33.7% (N = 103) and SIADH 32.4% (N = 99) were diagnosed most

Table 1. Demographic and clinical characteristics.

Variable	(N = 51)	Percentage %
Age (years)	68.3	SD = 13.0
Female	32	62.8
Co-Morbidities		
Diabetes	14	27.5
Hypertension	36	70.6
Heart Disease	14	27.5
Hypothyroid	10	19.6
Renal Failure	3	5.9
Medications		
Thiazide	10	19.6
SSRI	8	15.7
NSAID	27	52.9
ACEI/ARB	23	45.1
Procedure		
Total Knee Arthroplasty	17	33.3
Total Hip Arthroplasty	20	39.2
Irrigation/Debridement	7	13.7
Other	7	13.7
Elective Surgery	29	57.0
Emergent Surgery	22	43.0

SD = standard deviation. Heart Disease = coronary artery disease, heart failure, or atrial fibrillation; SSRI = selective serotonin reuptake inhibitors, NSAID—nonsteroidal anti-inflammatory drugs; ACEI—angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blocker; Other = nail fixation, shoulder arthroplasty, ankle open reduction and internal fixation.

frequently. The other categories included: hypotonic fluid 8.2% (N = 25), acute kidney injury 5.2% (N = 16), medications 5.9% (N = 18) and undetermined 14.7% (N = 45).

Agreement: Table 2

The three nephrologists agreed on the same etiology 43.1% (N = 22) of the time with a moderate overall interrater agreement, kappa = 0.43 (95% CI 0.34, 0.53).

The three internists agreed 35.3% (N = 18) of the time with a fair overall interrater agreement, kappa = 0.38 (95% CI 0.30, 0.46).

Overall agreement between all the doctors was fair, kappa = 0.39 (95% CI 0.35, 0.42).

4. Discussion

Diagnosing the underlying mechanism of postoperative hyponatremia is difficult. Multiple

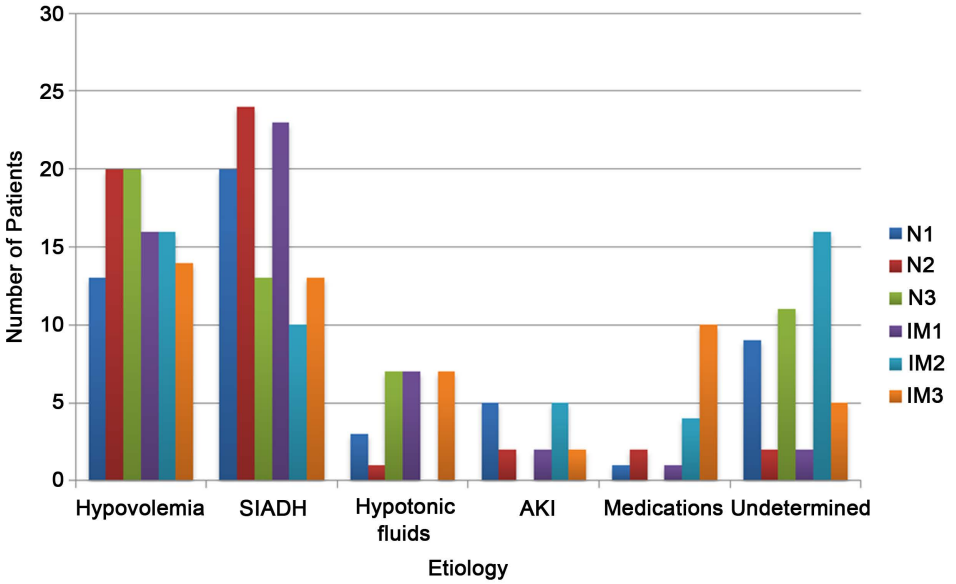

Figure 1. Etiologic diagnoses of post-operative hyponatremia determined by nephrologists and internists. Etiology of post-operative hyponatremia per three nephrologists (N) and three internists (IM). Key: N_1 = nephrologist 1; N_2 = nephrologist 2; N_3 = nephrologist 3; IM_1 = internist 1; IM_2 = internist 2; IM_3 = internist 3; AKI = acute kidney injury; SIADH= syndrome of inappropriate antidiuretic hormone.

Table 2. Nephrologist and internist interrater agreement.

Comparison	Kappa Coefficient (95% Confidence Interval CI)	Agreement
Nephrologists		
N_1 vs. N_2	0.45 (0.30, 0.60)	Moderate
N_1 vs. N_3	0.55 (0.40, 0.71)	Moderate
N_2 vs. N_3	0.32 (0.16, 0.49)	Fair
N_1 vs. N_2 vs. N_3	0.43 (0.34, 0.53)	Moderate
Internists		
IM_1 vs. IM_2	0.47 (0.31, 0.63)	Moderate
IM_1 vs. IM_3	0.33 (0.19, 0.48)	Fair
IM_2 vs. IM_3	0.37 (0.22, 0.53)	Fair
IM_1 vs. IM_2 vs. IM_3	0.38 (0.30, 0.46)	Fair
Inter-specialty		
N_1 vs. IM_1	0.73 (0.59, 0.87)	Substantial
N_1 vs. IM_2	0.40 (0.26, 0.55)	Fair
N_1 vs. IM_3	0.36 (0.21, 0.51)	Fair
N_2 vs. IM_1	0.41 (0.25, 0.57)	Moderate
N_2 vs. IM_2	0.18 (0.04, 0.32)	Slight
N_2 vs. IM_3	0.25 (0.10, 0.41)	Fair
N_3 vs. IM_1	0.54 (0.38, 0.70)	Moderate
N_3 vs. IM_2	0.31 (0.16, 0.47)	Fair
N_3 vs. IM_3	0.27 (0.10, 0.43)	Fair
Overall Agreement	0.39 (0.35, 0.42)	Fair

Key: Kappa Coefficient Interpretation: ≤0 poor; 0 - 0.02 slight; 0.21 - 0.40 fair; 0.41 - 0.60 moderate; 0.61 - 0.80 substantial; 0.81 - 1.0 almost perfect. N = nephrologist; IM = internist.

factors can be occurring simultaneously. Blood loss with resulting hypovolemia stimulates baroreceptors for AVP release. The process of surgery induces non-osmotic stimuli to AVP secretion through pro-inflammatory cytokines, positive pressure ventilation, nausea, hypoxia, hypercarbia, stress, pain and narcotics [6] [7]. In addition to AVP increasing the re-absorption of water in the collecting tubules of the nephron, limited peri-operative oral intake decreases the amount of solute needed for renal water excretion. Use of intravenous hypotonic fluids in all these situations will result in hyponatremia.

Our physician evaluators made diagnoses based on laboratory values and limited documented physical exam findings. The lab data was static, with no real time trend assessment. Oral and intravenous fluid intake was not known. Even when hyponatremia is assessed in real time, physicians struggle with defining the etiology. Clinical assessment of a patient's fluid status has a 50% accuracy rate [8] and diagnosis of hyponatremia by experienced clinicians has a 32% accuracy rate [4].

Hypovolemia and SIADH were most commonly diagnosed by our evaluators. Hyponatremia due to hypovolemia requires 0.9% saline infusion. However, infusing 0.9% saline in hyponatremia due to SIADH will cause further decline of the serum Na and worsen the hyponatremia. Rather, SIADH requires free water restriction. Laboratory values can assist in differentiating between the two. In contrast to SIADH, hyponatremia tends to have urine Na < 20 mmol/L, $FENa^+$ < 1%, uric acid >4 mg/dL [9] and a FEurea <12% [10]. But, because multiple mechanisms of hyponataremia may be occurring simultaneously in the post-operative state, laboratory values are not always so definitive. Measuring the rise or fall in serum Na after infusing 1 - 2 L of 0.9% saline can help differentiate the diagnoses. Measuring urine electrolytes prior to the infusion can help in predicting response. A urine Na ≤ 50 [11] or a urine Na + K/plasma Na < 0.5 [12] are more indicative of hypovolemic hyponatremia and suggest that serum Na will increase after the infusion of 1 - 2 litres of 0.9% saline. In SIADH, the serum Na will decrease further after infusion of 0.9% saline, especially if the osmolality of the administered fluid is less than the urine osmolality [12].

5. Conclusion

The two most frequent causes of orthopedic post-operative hyponatremia are hypovolemia and SIADH. It is important to differentiate between these two, since hypovolemic hyponatremia requires 0.9% saline resuscitation and SIADH hyponatremia requires fluid restriction. In both cases hypotonic fluids will lower plasma Na and should be avoided. Making the correct diagnosis can be difficult for both internists as well as nephrologists.

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International Journal of Clinical Medicine, 2016, 7, 675-684
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Pharmacist and Physician Collaborative Practice Model Improves Vancomycin Dosing in an Intensive Care Unit

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How to cite this paper: Levin, D., Glasheen, J.J. and Kiser, T.H. (2016) Pharmacist and Physician Collaborative Practice Model Improves Vancomycin Dosing in an Intensive Care Unit. *International Journal of Clinical Medicine*, **7**, 675-684.
http://dx.doi.org/10.4236/ijcm.2016.710073

Received: August 29, 2016
Accepted: October 22, 2016
Published: October 25, 2016

Abstract

Objective: A pharmacist and physician collaborative practice intervention to improve the initial dosing of vancomycin was implemented with the goal of decreasing the number of subtherapeutic first troughs and increasing the number of therapeutic troughs. **Methods:** Using the best available evidence, a nomogram was created to determine the initial vancomycin dose. The nomogram utilized actual bodyweight and glomerular filtration rate (eGFR) estimated with the MDRD4 equation. The dose was based on the 2009 ASHP/IDSA/SIDP guidelines, which recommended 15 - 20 mg/kg every 8 - 12 hours. Providers ordered "vancomycin IV dosed per pharmacy". **Results:** The pre- (n = 75) and post-intervention (n = 108) cohorts had similar age, gender distribution, weight, and eGFR. The median total daily vancomycin dose was similar in pre- and post-intervention groups (2000 mg), although the median first trough was higher following the intervention (13.0 vs. 14.8 mcg/ml, p = 0.03). Following the intervention, the proportion of first troughs under 10 mcg/ml decreased (32% to 13%, $p = 0.003$), while the proportion of troughs in the 10 - 20 mcg/ml therapeutic range increased (50.7% vs. 69.4%, $p = 0.01$). There was no difference in the proportion of troughs over 20 mcg/ml (17.3% vs. 17.6%, $p = 0.96$). **Conclusions:** A multi-disciplinary intervention utilizing a nomogram-based pharmacy collaborative practice model significantly improves the proportion of therapeutic initial vancomycin troughs and decreases the number of subtherapeutic troughs by half.

Keywords

Vancomycin, Nomogram, Protocol, Collaborative Practice,

Therapeutic Drug Monitoring

1. Introduction

Vancomycin is a glycopeptide antibiotic with activity against a variety of Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). It is commonly used as part of an empiric broad-spectrum antimicrobial regimen in critically ill patients. Vancomycin must be given intravenously when used for systemic infections, with dose adjustment for body weight and renal function [1].

Although there is a dearth of high-quality data on optimal dosing strategies for vancomycin, in 2009 the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) released joint consensus recommendations based on the best available evidence [1]. The expert panel recommended monitoring of steady-state vancomycin troughs with a goal level above 10 mcg/ml to avoid development of resistance. No preference was given to intermittent versus continuous dosing.

Vancomycin typically takes 36 - 48 hours to reach a steady state. If the initial dose is incorrect, a patient may be severely under- or overdosed for a considerable period of time with risk of treatment failure, development of antimicrobial resistance, or vancomycin toxicity. To mitigate this, several nomograms have been published, targeting troughs greater than 5 mcg/ml [2] and 7.5 mcg/ml [3]. However, these nomograms were published before the emergence of heteroresistant and vancomycin-intermediate *Staphylococcus aureus* (VISA) strains and the publication of joint consensus recommendations to keep troughs over 10 mcg/ml. The upper trough limit recommended in literature is 20 mcg/ml based on the American Thoracic Society (ATS) and IDSA guidelines on hospital-acquired pneumonia [4] and IDSA guidelines on bacterial meningitis [5].

Given the interpatient variability and complexity of vancomycin dosing in intensive care unit patients, utilizing a multidisciplinary approach to therapy could improve time to therapeutic target attainment and patient safety. Pharmacists have specialty training in pharmacokinetics and pharmacodynamics and have demonstrated improvements in drug utilization and patient outcomes in outpatient collaborative practice models [6] [7]. However, most inpatient studies evaluate the impact of pharmacists rounding with a multidisciplinary team [8], with few published studies evaluating inpatient pharmacy collaborative practice endeavors that fully delegate drug therapy management to the pharmacist.

We undertook a quality improvement initiative at our institution to optimize initial vancomycin dosing using a nomogram and a pharmacy collaborative practice approach. The primary objective was to decrease the number of subtherapeutic troughs due to antibiotic under dosing.

2. Methods

The study was performed at the University of Colorado Hospital, a tertiary academic

hospital. The study protocol was approved by the Colorado Multiple Institutional Review Board. Patient consent was not required and a Health Insurance Portability and Accountability Act waiver was obtained.

2.1. Vancomycin Nomogram Design

The nomogram was designed using current recommendations to dose vancomycin at 15 - 20 mg/kg every 8 - 12 hours in patients with normal renal function (**Table 1**) [1]. The decision to use intermittent rather than continuous dosing was based on the lack of definitive benefit with the latter, balanced by increased complexity and logistics such as the need for dedicated intravenous access in patients already receiving continuous infusions of vasopressors, sedatives, and analgesics. Actual body weight was used for dosing, including in obese patients, based on the best current evidence [9]. Although doses up to 6000 mg/day have been reported in literature [10], we capped the maximum initial dose at 4500 mg/day (1500 mg every 8 hours) for safety. Since vancomycin clearance is strongly tied to renal function [3], dosing every 8 hours was prescribed for patients with very high estimated glomerular filtration rate (eGFR). The eGFR was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD4) [11] equation using gender, age, creatinine, and race [$eGFR = 186 \times [\text{Serum Creatinine (mg/dL)}]^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if Female}) \times (1.210 \text{ if African American})$]. Vancomycin doses were rounded to 250 mg increments for dosing convenience. Therapeutic trough range was defined as 10 - 20 mcg/ml. This trough range was designed to yield an Area Under the Curve to Minimum Inhibitory Concentration (AUC:MIC) ratio of > 400 in the majority of patients, because the *Staphylococcus aureus* MIC at the University of Colorado Hospital is typically ≤1 mcg/ml.

Table 1. Vancomycin nomogram.

eGFR (ml/min/1.73 m^2)	Actual bodyweight (kg)			
	<60	60 - 80	81 - 100	>100
>90	750 mg q8	1000 mg q8	1250 mg q8	1500 mg q8
50 - 90	750 mg q12	1000 mg q12	1250 mg q12	1500 mg q12
15 - 49	750 mg q24	1000 mg q24	1250 mg q24	1500 mg q24
<15 or RRT	750 mg ×1	1000 mg ×1	1250 mg ×1	1500 mg ×1

Therapeutic drug monitoring

1. For patients dosed every 8 - 12 hours, check trough 30 minutes prior to 4th dose
2. For patients dosed every 24 hours, check trough 30 minutes prior to 3rd dose

Patients with eGFR < 15, continuous RRT, or unstable renal function

1. Give a one-time dose per nomogram
2. Check a random vancomycin level 24 hours after the dose
3. If random level is <20 mcg/mL, repeat dose
4. If random level is >20 mcg/mL, do not redose, repeat random level in 12 hours

Patients on intermittent hemodialysis

1. Give a one-time dose per nomogram
2. Check a random vancomycin level 2 hours after hemodialysis
3. If random level is <20 mcg/mL, repeat dose
4. If random level is >20 mcg/mL, do not redose, repeat level after next dialysis

Dosing frequency is in hours (q8 = every 8 hours; q12 = every 12 hours; q24 = every 24 hours). eGFR = estimated glomerular filtration rate; RRT = renal replacement therapy.

2.2. Collaborative Practice Implementation

The vancomycin nomogram and the collaborative practice protocol were reviewed and approved by the University of Colorado Hospital Pharmacy and Therapeutics committee and were implemented per the Colorado State Boards of Medicine and Pharmacy collaborative practice model agreement. All clinical pharmacists involved in care of ICU patients were trained in nomogram use with a mandatory online educational module. Prescribing providers in ICUs were given a copy of the protocol and instructed to order "vancomycin IV dosed per pharmacy" rather than indicate dose and frequency, although providers were also allowed to override the protocol and order a different dose at their discretion. A clinical pharmacist then gathered the required demographic and laboratory information, calculated eGFR, and ordered the vancomycin dose from the nomogram. Additionally, the pharmacist ordered a vancomycin trough at an appropriate time prescribed per the protocol. Vancomycin pharmacokinetic tracking forms were reviewed on a weekly basis during the study period.

2.3. Patient Population

Adult patients started on vancomycin in the intensive care unit (ICU) were included regardless of body weight and renal function, including renal replacement therapy. Patient demographics, actual bodyweight, vancomycin dose, and vancomycin trough data was obtained from pharmacokinetic tracking forms filled out prospectively by ICU clinical pharmacists. Only patients without a measured vancomycin trough concentration were excluded from the study. Patients were divided into historical control and intervention groups. Historical data was obtained from records of patients treated during the 3 months prior to protocol initiation. Patients in the intervention group were treated under the collaborative practice protocol for the 6-month period post protocol initiation.

2.4. Outcomes Evaluated

The primary outcome of this study was the incidence of subtherapeutic initial vancomycin trough concentrations, defined as a first drawn steady-state trough value < 10 mcg/ml [1]. Secondary outcomes evaluated were the percentage of initial trough concentrations in goal range (10 - 20 mcg/ml), percentage of supratherapeutic trough concentrations (>20 mcg/ml), and the median daily vancomycin dose. Outcomes were compared between historical controls and the intervention group.

2.5. Statistical Analysis

Assuming subtherapeutic values in 34% of vancomycin trough concentrations (< 10 mcg/ml) in the historical control group, a total of 70 patients were needed in each group to have an 80% power to detect a 20% absolute decrease in subtherapeutic vancomycin trough concentrations.

Statistical analysis of the results was performed with Microsoft Excel (Microsoft, Redmond, WA) and Statext 1.4.1 (Statext.com). Continuous variables were compared using the Mann-Whitney U test and the Kruskal-Wallis one-way analysis of variance.

Categorical variables were compared using the Fisher's exact test and the chi-square test for independence. All tests were 2-tailed. A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics

A total of 183 patients were enrolled in this study: 108 in the collaborative practice group and 75 in the historical control group. The suggested nomogram dosing regimen was used in 108/178 (60.1%) of eligible patients during the intervention period. Demographics of the 75 historical controls and the 108 patients dosed under the collaborative practice agreement are shown in Table 2.

3.2. Evaluation of Vancomycin Trough Concentrations

Although there was no statistically significant difference in the median total daily dose of vancomycin, the intervention group had a significantly higher median initial trough (14.8 mcg/ml, IQR 11.6 - 18.2, vs. 13.0 mcg/ml, IQR 9.1 - 16.8, $p = 0.03$). The intervention group experienced a significant reduction in the proportion of subtherapeutic

Table 2. Patient characteristics at vancomycin initiation.

Variable	Controls (n = 75)	Non-users (n = 70)	Intervention (n = 108)	*p*-value
Age (years)	56 (47 - 64)	52 (39 - 62)	53 (42 - 64)	$p = 0.4$
Male sex (%)	56	59	56	$p = 0.9$
Actual bodyweight (kg)	85 (66 - 97)	88 (64 - 107)	78 (67 - 96)	$p = 0.7$
<60 kg	13%	20%	10%	$p = 0.2$
60 - 80 kg	25%	20%	46%	$p < 0.005$
81 - 100 kg	40%	29%	21%	$p = 0.02$
>100 kg	21%	31%	22%	$p = 0.3$
eGFR (ml/min/1.73 m^2)	89 (56 - 109)	81 (54 - 114)	70 (47 - 102)	$p = 0.2$
<15 or RRT	12%	24%	15%	$p = 0.1$
15 - 49	19%	11%	19%	$p = 0.4$
50 - 90	32%	24%	39%	$p = 0.1$
>90	37%	40%	28%	$p = 0.2$
Vancomycin TDD (mg)	2000 (2000 - 2250)	2000 (1250 - 3000)	2000 (1250 - 2500)	$p = 0.5$

Data presented as proportions or median (interquartile range). eGFR = estimated glomerular filtration rate; RRT = renal replacement therapy; TDD = total daily dose.

troughs < 10 mcg/ml (32.0% to 13.0%, $p = 0.003$), a significant increase in the number of in-range troughs 10 - 20 mcg/ml (50.7% to 69.4%, $p = 0.01$), and no significant change in supratherapeutic troughs > 20 mcg/ml (17.3% to 17.6%, $p = 0.96$) compared to historical control patients (Figure 1). The 70 patients who were not dosed using the collaborative practice option during the intervention period had a trough distribution similar to historical controls (27.1% low, 51.4% in-range, and 21.4% high; $p = 0.02$ for proportion of low and in-range groups compared to the collaborative practice nomogram cohort, $p = 0.5$ for comparison of supratherapeutic groups).

3.3. Evaluation of Vancomycin Troughs in Weight and eGFR Subgroups

The nomogram also performed well in subsets of patients at the extremes of weight and renal function (Table 3). Compared to historical controls and collaborative practice non-users, the intervention group had more patients with therapeutic troughs among those weighing 60 - 80 kg ($p = 0.01$). There was a trend towards significant improvement in therapeutic troughs in subgroups with body weight under 60 kg ($p = 0.05$) and eGFR > 90 ml/min/1.73 m^2 ($p = 0.08$).

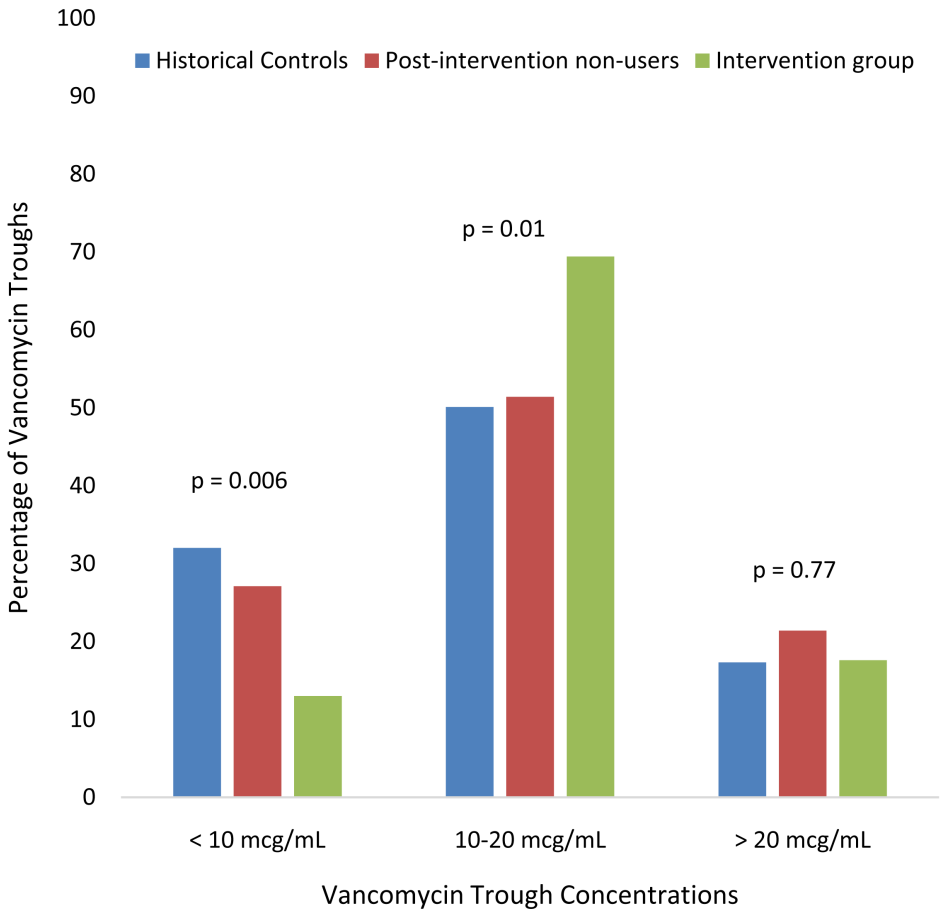

Figure 1. Distribution of initial vancomycin troughs among historical controls, patients not dosed per nomogram during the intervention period (non-users), and patients dosed using the collaborative intervention nomogram.

Table 3. Proportion of vancomycin troughs in therapeutic (10 - 20 mcg/ml) range in historical controls, nomogram non-users, and nomogram-dosed patients at the extremes of weight and renal function.

	Controls	Non-users	Intervention	*p*-value
	(n = 75)	(n = 70)	(n = 108)	
Actual bodyweight (kg)				
<60	4/10 (40%)	5/14 (36%)	9/11 (82%)	p =0.05
60 - 80	6/19 (32%)	7/14 (50%)	36/50 (72%)	p = 0.01
81 - 100	18/30 (60%)	10/20 (50%)	14/23 (61%)	p = 0.7
>100	10/16 (63%)	14/22 (64%)	16/24 (67%)	p = 0.9
eGFR (ml/min/1.73 m^2)				
<15 or RRT	5/9 (56%)	9/17 (53%)	12/16 (75%)	p = 0.4
15 - 49	8/14 (57%)	6/8 (75%)	14/20 (70%)	p = 0.6
50 - 90	12/24 (50%)	9/17 (53%)	28/42 (67%)	p = 0.4
>90	13/28 (46%)	12/28 (43%)	21/30 (70%)	p = 0.08

eGFR = estimated glomerular filtration rate; RRT = renal replacement therapy.

4. Discussion

We have demonstrated that a physician and pharmacist collaborative practice-based quality improvement initiative utilizing an evidence-based nomogram can successfully improve initial vancomycin dosing in critically ill patients. Our primary objective was to minimize the risk of underdosing and subsequent promotion of antimicrobial resistance, and in that respect 87% of patients dosed with the nomogram had an initial trough ≥10 mcg/ml. Although our nomogram was only 69% successful in reaching the therapeutic range of 10 - 20 mcg/ml, this is significantly better than provider-initiated dosing at our institution (44% - 51%) and in published studies of non-nomogram dosing (34%) [12]. While another previously published nomogram was 94% accurate [2], it targeted a much broader trough range of 5 - 20 mcg/ml. Accuracy of our protocol might have been adversely affected by the dynamic nature of ICU patients. Vancomycin clearance is strongly tied to renal function and since critically ill patients often have dynamic renal function, pinpointing an accurate eGFR can be challenging.

We observed a significant increase in the median vancomycin troughs without a corresponding change in the median total daily dose, as well as a decrease in subtherapeutic troughs without a concurrent increase in supratherapeutic troughs. This supports that patients were dosed more correctly for their bodyweight and renal function rather than simply receiving a higher dose across the board. The fact that provider-initiated dosing during the intervention period did not significantly differ from the historical controls favors the improvement being due to implementation of the nomogram.

It is important to note that our historical and non-user groups significantly differed from the nomogram cohort in certain weight subgroups. It is unclear whether this reflects our small sample size, a seasonal variation in ICU patients, or both. Unfortunate-

ly, analysis of all subgroups was limited by small sample size and a Type II error cannot be ruled out. Nevertheless, our data suggest improvement due to use of the nomogram in patients weighing less than 80 kg, and a trend toward significance with eGFR > 90 ml/min/m^2.

Additional limitations of this study include a small sample size, application at a single hospital, and lack of clinical and microbiologic outcome data. *Staphylococcus aureus* MICs at our institution are typically ≤1 mcg/ml, so our nomogram was not directly designed to achieve the narrower trough serum concentration of 15 - 20 mcg/ml in all patients. Patients were only enrolled from the medical intensive care unit, so the applicability of our nomogram to other patient populations is unknown.

A large number of patients during the intervention period were dosed without the nomogram. This reflects the inherent challenge of implementing quality improvement initiatives that rely on changing behavior. Prior to the collaborative practice model, we attempted to educate providers to directly use the nomogram with a nearly zero-use rate despite frequent personal communication with physicians. Following roll-out of the collaborative practice, providers chose to bypass this process even though ordering "vancomycin per pharmacy" was easier than ordering a specific dose. We do not know if this was done for reasons of clinical judgment or because they did not know that this option was available. If clinical judgment was the reason for non-adherence, our findings of the non-nomogram group performing comparably to controls identify a potential knowledge and skill gap. Although clinical pharmacists were encouraged to call providers to encourage them to use the nomogram, this did not reliably happen because of workload issues and logistics.

In the course of this project, we were reminded of the scarcity of high-quality data on vancomycin dosing. With the advent of vancomycin-intermediate heteroresistant pathogens, a minimum trough of 15 mcg/ml may be required to avoid treatment failures. The narrow therapeutic range of 15 - 20 mcg/ml would be exceedingly difficult to attain even with the best dosing practices and high-quality research is urgently needed to establish the safe upper limit for vancomycin doses using the modern formulation of the antibiotic.

Finally, this study demonstrates that a physician and pharmacist collaborative practice model lends itself well to medications with complex dosing and monitoring requirements and should be explored as an effective quality improvement solution.

5. Conclusion

Utilization of an inpatient pharmacy collaborative practice model to manage vancomycin therapy resulted in a significant reduction in subtherapeutic trough concentrations and increased the percentage of therapeutic trough concentrations. This was accomplished without increasing the percentage of supratherapeutic trough concentrations. This inpatient multidisciplinary collaborative practice model should be evaluated in broader drug categories and patient populations to ensure reproducibility of these findings.

Acknowledgements

The authors would like to acknowledge Gerry Barber, RPh MPH, Michelle Barron, MD, Larry Golightly, PharmD, and Jonathan Pell, MD, for their assistance in design and implementation of this project. The authors acknowledge the following University of Colorado Hospital physicians and pharmacists for participating and contributing to the success of the collaborative practice model: Craig Anthony, PharmD, Bonnie Boller, PharmD, Ellen Burnham, MD, Sarah Carson, PharmD, Lisa Dufficy, PharmD, Douglas Fish, PharmD, Dennise Luby, PharmD, Robert MacLaren, PharmD, Scott Mueller, PharmD, Deborah Sherman, PharmD, Cathryn Todd, PharmD, Jessica Wittmer, PharmD, and the University of Colorado physicians and housestaff

Preliminary data presented in poster format at: The Society of Hospital Medicine Annual Meeting 2010, Abstract #87. Levin D., Kiser T. A Multidisciplinary Intervention Improves Vancomycin Dosing in the Intensive Care Unit [abstract]. Journal of Hospital Medicine, 2010, 5 (suppl 1), http://www.shmabstracts.com/abstract/a-multidisciplinary-intervention-improves-vancomycin-dosing-in-the-intensive-care-unit/.

Conflict of Interest

The authors declare that they have no conflict of interest.

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International Journal of Clinical Medicine, 2016, 7, 685-689
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Grape Seed Extract and the Fetal Ductus Arteriosus: A Potential Danger of a Common Herbal Supplement

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How to cite this paper: Benjamin, B., Schamberger, M. and Ebenroth, E. (2016) Grape Seed Extract and the Fetal Ductus Arteriosus: A Potential Danger of a Common Herbal Supplement. *International Journal of Clinical Medicine*, **7**, 685-689.
http://dx.doi.org/10.4236/ijcm.2016.710074

Received: July 22, 2016
Accepted: October 24, 2016
Published: October 27, 2016

Abstract

A female at 28 weeks gestation was referred to pediatric cardiology for a fetal arrhythmia. The echocardiogram revealed premature constriction of the fetal ductus arteriosus. Her work up was unremarkable except for her use of an herbal supplement, grape seed extract, which is advertised as a potent anti-inflammatory medication, and has biochemical properties similar to other medications that have been shown to cause premature ductal constriction. The use of herbal remedies increases each year. Although the public is inundated with radio, television, and internet advertisements for these products, little unbiased information regarding the possible dangers of toxicity or adverse reactions exists. As physicians, we need to be aware of these products, and counsel our patients accordingly.

Keywords

Grape Seed Extract, Prenatal Medications, Ductus Arteriosus, Cardiology, Herbal Remedies

1. Introduction

In a recent study, more than one-third of Americans polled reported trying some form of alternative medicine at least once [1]. This is hardly surprising since homeopathy is a familiar concept to older Americans, many of whom grew up taking home-grown family cold and flu remedies. The younger generation, although accustomed to more conventional medical management, is continually flooded with television and magazine advertisements declaring the medical efficacy of "natural" treatments. In addition, widespread use of the internet makes both the information and the availability of homeo-

pathic medications readily accessible to cyber-savvy patients. Very few websites, however, offer consumers accurate and unbiased information regarding the potential dangers of toxicity or adverse reactions from these products. Although many herbal supplements are harmless in sensible doses, some may exhibit unfavorable or even toxic effects in certain patient populations. We will present a case that illustrates constriction of the fetal ductus arteriosus associated with maternal consumption of grape seed extract, a common homeopathic supplement. Informed consent was not obtained prior to the writing of this report.

2. Case

A 36-year-old G2, P1 at 28 weeks gestation was referred to Pediatric Cardiology for a fetal echocardiogram due to a fetal arrhythmia detected during a routine sonogram. She was rubella immune, VDRL nonreactive, hepatitis B surface antigen negative, and group B streptococcus negative. There was no history of maternal infections and she initially reported taking no medications during this pregnancy. Due to advanced maternal age, an amniocentesis was performed during the second trimester and revealed a normal 46 XX fetus with no detectable chromosomal abnormalities. The mother's past medical history was significant only for mild aortic regurgitation. She denied any use of tobacco, alcohol, or recreational drugs. The fetal echocardiogram revealed a structurally normal heart, but was significant for constriction of the ductus arteriosus (Figure 1). There was right-to-left shunting with Doppler velocity of 1.5 m/sec indicating premature ductal constriction. No fetal arrhythmia was detected. Upon further questioning about diet and medication practices, she denied use of non-steroidal anti-inflammatory drugs (NSAIDs) but admitted to taking grape seed extract. Her husband was a staunch believer in homeopathy and he encouraged her to take the herbal supplement because

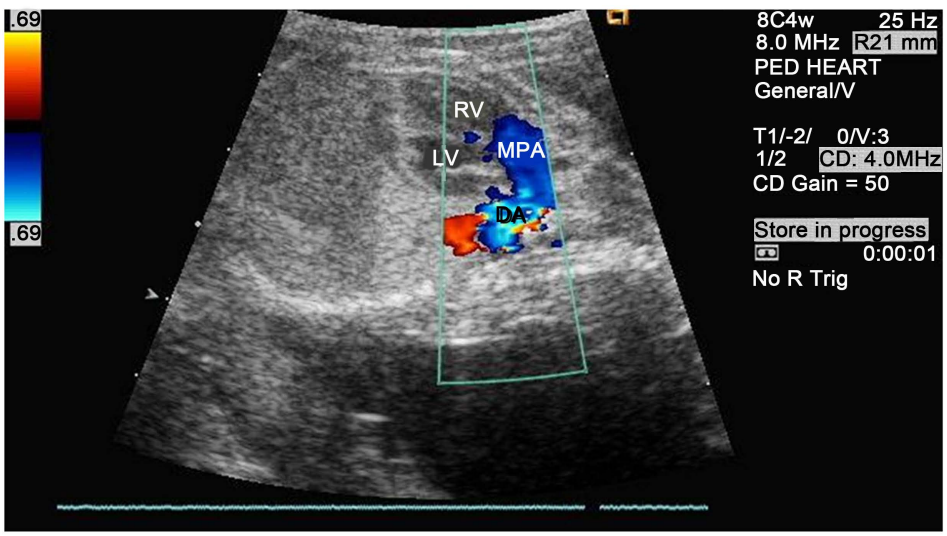

Figure 1. 2D/Color Doppler fetal echocardiographic image showing turbulence in the ductus arteriosus consistent with premature ductal construction. RV: right ventricle, LV: left ventricle, MPA: main pulmonary artery, DA: ductus arteriosus.

he felt it would "be good for her heart." It is unclear as to how long she had been taking the supplement prior to presentation. She was advised by the echocardiography physician to discontinue her use of the grape seed extract. A repeat fetal echocardiogram four weeks later at 32 weeks gestation revealed worsening premature ductal constriction with a Doppler velocity of 1.8 m/sec. Although she claimed to have discontinued use of the grape seed extract, her furtive glances at her husband, and his vehement, bordering on belligerent, insistence that these substances are "natural and perfectly safe", when questioned as to whether she had stopped taking the product, suggested otherwise.

They refused to return for follow up fetal echocardiography and the pregnancy progressed without further complications. The patient gave birth to a healthy, term-baby via uncomplicated spontaneous vaginal delivery. The neonate weighed 3.6 kg and had Apgar scores of 8 and 9 at 1 and 5 minutes respectively and was discharged home with the mother on postpartum day of life two without complications.

3. Discussion

During fetal life, the ductus arteriosus shunts blood from the pulmonary circulation to the systemic circulation. Direction of fetal ductal flow is determined by low resistance within the aortic (umbilical-placental) circulation and high resistance within the pulmonary artery circulation. Immediately following the first breath at birth, the lungs expand and pulmonary vascular resistance drops. The pressure gradient along the ductus reverses as the pulmonary circulation becomes the low pressure system and the systemic circulation becomes the high pressure system. As a result, there is a reversal of flow within the ductus, exposing the vessel to oxygenated blood. The increased oxygen tension predisposes the ductus to constriction. Once the umbilical cord is cut, the ductus loses the placental source of vasodilators and the remaining prostaglandins in the circulation are quickly metabolized within the lungs [2]. Functional closure of the ductus typically occurs within 10 to 18 hours and is mediated by constriction of smooth muscle cells. Severe constriction or functional closure of the ductus arteriosus before birth can lead to pulmonary hypertension, which can be a source of severe post-natal morbidity and death [3].

Grape seed extract contains a variety of compounds, the most important of which are the bioflavonoids and procyanidins. According to recent research, these natural compounds possess antioxidant and free radical scavenging activity that may prove useful in the treatment of a variety of illnesses [4]. Additionally, advertisements claim that grape seed extract possesses potent anti-inflammatory activities. Studies have demonstrated that the anti-inflammatory activity of the procyanidins works through inhibition of prostaglandin production by direct inhibition of the enzyme cyclooxygenase [5]. This is the same mechanism of action found in the class of drugs known as NSAIDs. It has been previously shown in both animal and human studies that inhibition of prostaglandin synthesis during pregnancy produces premature ductal constriction [6] [7]. Koren *et al.* demonstrated that the use of NSAIDs in pregnant women was associated

with a 15-fold increase in the incidence of premature ductal constriction [8].

The manufacturers of herbal remedies and supplements in the United States are not federally regulated like the pharmaceutical industry. Consequently, many unsubstantiated claims are made concerning the benefits of these substances, and the companies are not required to list or report any potential adverse effects. The American Academy of Pediatrics had shown support for the Dietary Supplement Information Act, which would have required tighter federal regulation of all dietary supplements [9]. Under this act, all involved in the manufacture, packing, and distribution of dietary supplements would have been required to register with the FDA, submit a product label for approval, and report any adverse effects associated with their products. Unfortunately, this act was never passed into law.

This is the first reported case in which a dietary supplement taken by a pregnant patient may have resulted in constriction of the fetal ductus arteriosus. Although the patient was instructed to discontinue taking the grape seed extract, the clinical picture and the results of the second fetal echocardiogram were highly suggestive of her noncompliance. Be that as it may, this case illustrates the potential adverse effects that can be caused by "natural" dietary supplements. Until the federal government begins to regulate herbal remedies and dietary supplements, and mandates reporting of adverse events, physicians and consumers alike need to view these products with caution.

The case demonstrated the potential dangerous effects that herbal remedies can have on a pregnancy. As most patients do not consider these products to be medications, physicians must routinely inquire about their patients' diet, and specifically about dietary supplement use, when taking a detailed history. It is important for physicians to be aware of these products and of potential side effects that can occur from their use in order to properly educate their patients. Physicians should emphasize that the effects of natural supplements are, at present, not fully understood and that one should seek appropriate medical advice before purchasing or taking herbal remedies, just as one would for prescription or non-prescription medications.

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International Journal of Clinical Medicine, 2016, 7, 690-697
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Breast Core-Needle Biopsy in a Large Tertiary Oncologic Centre—1-Year Experience after the Introduction of the Method

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How to cite this paper: Brnić, Z., Marinkić, M., Schmidt, S., Pedišić, I. and Bolanča-Čulo, K. (2016) Breast Core-Needle Biopsy in a Large Tertiary Oncologic Centre—1-Year Experience after the Introduction of the Method. *International Journal of Clinical Medicine*, **7**, 690-697.
http://dx.doi.org/10.4236/ijcm.2016.710075

Received: August 10, 2016
Accepted: October 24, 2016
Published: October 27, 2016

Abstract

Ultrasound (US)-guided core-needle biopsy (CNB) is currently the procedure of choice for work-up of suspicious breast lesion. It is mainly used for evaluation of suspicious breast lesions categorized as BI-RADS 4 and 5 (Breast Imaging-Reporting and Data System). The conducted study included 56 female patients with detected suspicious breast leasions, and they underwent US-guided CNB during 1-year period with the aim to investigate the value of US-guided CNB of the breast in a tertiary-level large-volume oncological centre setting with respect of indications, technical adequacy and safety. 2 patients who entered the study were previously diagnosed as BIRADS 2, 3 patients as BIRADS 3, 18 patients as BIRADS 4 and 33 patients as BIRADS 5. In 14 patients with BC (breast cancer), both FNA (fine-needle aspiration) and CNB were performed, and the malignancy was accurately diagnosed by cytology in 9 patients, confirmed by subsequent CNB in all of them. ADH (atypical ductal hyperplasia) was initialy diagnosed by FNA in 5 patients, and in 2 of them, BC was initialy missed by FNA, but deteced by CNB. As it is known, the cytology has lower sensitivity for detection of BC than hystology, with false-negative rate ranging from 2.5% to 17.9%. In our material, 18.7% of carcinomas were initialy left undetected by FNAC, and subsequently confirmed by CNB. All confirmed carcinomas were correctly suspected on imaging, and categorized as BI-RADS 4 or 5, while all BI-RADS 2 and 3 findings were confirmed as benign on hystology. False-positive rate of imaging was 8%. An average number of 4 tissue cores (range: 2 - 7) was taken in our experience if good quality of the first 3 core was achieved, and there was no consistent reason to proceed with sampling.

Keywords

Breast Cancer, US-Guided Core Needle Biopsy (CNB), Suspicious Breast Lesion, Tissue Core

1. Introduction

Breast cancer (BC) is one of the most common malignant tumors and an important cause of cancer-related deaths among women. Mammography (MG) is still considered to be the best screening test for BC, with breast ultrasound (US) as the most appropriate complementary imaging modality [1] [2]. First described by Parker *et al*. in the early 1990s, US (ultrasound)-guided core-needle biopsy (CNB) is currently the most accurate method of tissue-sampling, and is the procedure of choice for work-up of US-detected suspicious breast lesion [3].

CNB is recognized as a reliable alternative to surgical biopsy for obtaining histologic diagnosis, commoly used for evaluation of suspicious breast lesions categorized as BI-RADS 4 and 5 (Breast Imaging-Reporting and Data System) [4] [5], valuable also in cases of undeterminate or probably benign lesions [6] [7] [8]. US-guided CNB has high sensitivity (97.5%) in the detection of BC, and many advantages such as high safety due to real-time needle guidance and lack of radiation, possibility of evaluation of tumor grade and receptors, good patient comfort, wide availability, acceptable time consumption and more than fourfold lower costs than surgical biopsy in Croatia (official health service price-list, Croatian Health Insurance Office, 2015). However, an important limitation includes unability to biopsy lesions not clearly detectable by US such as microcalcifications and architectural distortions. Such lesions should be identified and targeted either stereotactically or by use of MRI, in order to avoid a false negative outcomes [3] [7]-[13].

US-guided CNB is a well-established procedure only in large clinical centres in Croatia, while in many mid-size and smaller county hospitals, the method is yet not accepted, mainly due to the lack of qualified personel. Retrospective study performed in the largest Croatian hospital centre, which included imaging-histological concordance analysis, revealed high accuracy, low percentage of false-negative results and high safety of the procedure [14].

Our study aimed to investigate the value of US-guided CNB of the breast in a tertiary-level large-volume oncological centre setting with respect of indications, technical adequacy and safety.

2. Materials and Methods

The study included 56 female patients with detected suspicious breast leasions, who underwent US-guided CNB during 1-year period (September 2014-October 2015). Breast CNB was performed as part of the *tripple assessment* routinely applied in the institution. In selected cases the fine-needle aspiration (FNA) with cytological analysis was done prior to CNB, particularly in patients with clinical suspicion of neoplasm but without imaging findings suggestive of BC, and patients with probably benign imaging findings (BIRADS 3) and no evidence of increased risk for BC. Informed consent before the procedure was mandatory for every patient.

US-guided CNB of the breast—the procedure: The women were placed in the supine position with ipsilateral upper limb resting behind their heads. After the patients' skin

was prepped and the target area covered with sterile drapes, the radiologist performed the puncture using the "freehand technique", holding the transducter with one hand while identifying the target lesion and manipulating the spring-loaded CNB device with the other hand. Under US-guidance 2-5 mL of lidocaine was injected along the presumed needle pathway. A small skin nick was made at the needle entry site, and the biopsy needle was inserted. Disposable HTC device (HUNTER Automatic guillottine system, Tsunami Medical, Italy) with 10 or 15 cm long 14-G needle with 22-mm throw was used for all procedures. The oblique approaching pathway of the needle, with consequent parallel needle position to the chest wall during firing was preferred in order to provide good visualisation of the needle and to assure the best safety. After the CNB device was fired, the needle tip was identified inside the mass, and image was recorded to document the correct targeting. The adequacy of tissue samples was visually checked for integrity and colour. Each specimen was put into the 10%-buffered formaldehyde solution, checked for floating (predominantly fat tissue) or sinking (presumably glandular and/or fibrous tissue), and sent to pathology for analysis.

The referring diagnoses, distribution of BI-RADS categories, reasons for US-guided CNB, and diagnostic outcome after tissue sampling were shown in percentages and discussed. The length of tissue cores was measured by ruler. The number of cores per procedure was analysed. The quality of tissue cores were visualy analysed for floating in the formaldechyde solution, integrity (fragmentation) and bloodiness. Pathologist's observations upon inadequacy of sampling material were considered.

3. Results and Discussion

Fifty-six patients (58.7 years, range 37 - 80, 48.2% premenopausal) were included in our series. The patients were referred to our hospital by breast surgeons, oncologists or family doctors with the request to get breast CNB performed. No special preparation was proposed, except anticoagulants or aspirin withdrawal 3 days prior to procedure. **Table 1** shows referring diagnoses from request forms for the patients which underwent US-guided CNB. In the vast majority of cases the indication for CNB was based on clinical and/or radiological suspicion of breast malignancy. Relatively high proportion of referring diagnoses reflected disease non-confined to the breast (39/67, 58.2%), while 46.4% (26/56) patients was assigned a simple clinical diagnose *breast neoplasm*, without any other specification. In 22/56 (39.2%) of women lymph node metastases were clinicaly suspicious (18 cases of axillary, and 4 cases of other regional lymphadenopathy). In 1 patient CNB was indicated after cytological detection of atypical ductal hyperplasia (ADH) in fine-needle aspiration (FNA) material [15] [16].

The distribution of BI-RADS categories of patients underwent US-guided CNB was shown in **Table 2**. There was no patients assigned as BI-RADS 0 or 1 in our material, meaning that CNB was not done in patients with incomplete diagnostic work-up or in patient in which imaging was normal, even if clinical finding was suspicious. BIRADS 0 category requires either repeat of MG or further imaging study(ies), hence no CNB is indicated [4]. In our institution the patients without imaging findings suggestive of

Table 1. Referring diagnoses assigned to patients submitted to US-guided CNB.

Referring diagnosis	Number of patients	Comment/remark
Breast cancer (BC) (without other specification)	26	
Bilateral BC	6	
Inoperative/exulcerated BC	7	
Inflammatory BC	1	
BC with enlarged axillary nodes	18	
BC with enlarged neck nodes	2	
BC with enlarged supraclavicular nodes	2	
BC with distant metastases	2	
BC with infiltration of pleura	1	
Fibroadenoma	1	Palpatory suspect, enlarging
Mastopathia	1	Palpatory suspect, atypical ductal hyperplasia detected by cytology
Total number of diagnoses	**67**	Some patients were assigned with more than one referring diagnose

Table 2. BI-RADS categories of patients underwent US-guided CNB: the highest US, MG or MR BI-RADS category was taken into account if more than one imaging modality were done prior to CNB.

Imaging category	Number of patients	Comment/remark
BIRADS 2	2	Palpatory suspect
BIRADS 3	3	
BIRADS 4	18	
BIRADS 5	33	
Total number of patients	**56**	

neoplasm, but with palpatory suspicion of malignancy undergo FNA as only primary sampling method. Two BI-RADS 2 patients with palpatory suspicious breast lump had equivocal FNA findings from other institution, and were biopsied following the request of other doctors, which thought that the findings were of limited accuracy. Very low proportion of BI-RADS 3 patients in our material (3/56, 5.4%) reflects the practice that patients with probably benign breast lesions are commonly submitted to US-guided FNA, and regular US follow-up in 6-months periods [5]. BI-RADS 5 is the most frequent category in our series (33/56, 58.9%) as clinicaly and radiologicaly clearly malignant or advanced breast neoplasms tend to cumulate in our specialized national oncology centre in which a wide spectrum of diagnostic and treatment options are readily available for patients with BC.

Reasons for US-guided CNB were specified in Table 3. Remarkable proportion of patients (28/56, 50%) were candidates for neoadjuvant therapy, and CNB is mandatory

Table 3. Reasons for US-guided CNB.

Reasons for biopsy	Number of patients
Preoperative PHD	24
Neoadjuvant therapy planned	28
Other reasons	4
Total number of patients	**56**

for such patients as it enables proper choice of the best antineoplastic agent [17]. The category *other reasons* include inconclusive FNA findings and lesions suspected by MR detectable also by US.

In the subgroup of 14 patients with BC both FNA and CNB were performed, and the malignancy was accurately diagnosed by cytology in 9 patients, confirmed by subsequent CNB in all of them. ADH was initialy diagnosed by FNA in 5 patients, and in 2 of them BC initialy missed by FNAC was subsequently found at hystology. As it is known, the cytology has lower sensitivity for detection of BC than hystology, with false-negative rate ranging from 2.5% to 17.9%. In our material 18.7% of carcinomas were initialy left undetected by FNAC, and subsequently confirmed by CNB, which is not significantly different from the results in the literature [15] [16] [18].

Table 4 shows histological diagnoses obtained from CNB in comparison to imaging findings. As expected, the majority of tumors were invasive ductal carcinomas, and only 2 tumors of lobular origin were found. All carcinomas confirmed by hystology were correctly suspected on imaging, and categorized as BI-RADS 4 or 5. All BI-RADS 2 and 3 findings were confirmed as benign on hystology; these patients were proceeded to CNB because of palpatory suspicion for malignancy. False-positive rate of imaging was 8%, as a result of 2 false-positive MRI findings and 2 false-positive MG findings.

With each CNB procedure, an average number of 4 tissue cores (range 2 - 7) were taken from different parts of the US-detectable lesion. The central, possibly necrotic areas of the tumor were consistently avoided from targeting. The length of tissue cores in our material ranged 19 - 23 mm.

No cores obtained in our material was considered by pathologist as inadequate for hystological analysis, hence no re-biopsies were requested neither by pathologist nor by clinician. Other authors report up to 10% of re-biopsies in their material [14] [19] [20]. We observed fragmentation in 27% of cores, which did not compromised the value of CNB. First obtained tissue core was of the best quality in 49/56 (87.5%) of cases, while subsequent cores were more or less blood, as the destruction of the breast architecture, and local haemorrhage occurs. The last tissue core was bloody and fragmentated in 33/56 (58.9%) of procedures.

European guidelines are not too dogmatic about the number of cores, realizing that variablity can be accepted between cases and operators [21]. We think that even a single core may be sufficient for the diagnosis of a solid mass, if the radiologist is confident of sampling adequacy. If good quality of the first 3 core was achieved, there was no consistent reason to proceed with sampling in our experience. This may differ from the

Table 4. Pathophysiological diagnoses (PHD) obtained from CNB in comparison to imaging findings.

PHD	Number of patients	BI-RADS 4 or 5	BI-RADS 2 or 3
Invasive ductal carcinoma	44	44	0
Lobular carcinoma in situ	1	1	0
Invasive lobular carcinoma	1	1	0
No tumor	10	4*	6**
Total number of patients	**56**	**50**	**6**

*MR BI-RADS 4 in 2 patients, MG BI-RADS 4 in 2 patients; **palpatory suspicious BI-RADS 2 in 3 patients, BI-RADS 3 in 3 patients.

opinion that larger core number is necessary [6] [22]. The higher the number the cores, the higher representativeness of the material in the sense of accurate targeting the lesion of interest. Hovewer, our patients had relatively large tumors, and no risk of off-target cores existed, hence even limited number of samples seemed to be acceptable. With small lesions, even more than 4 cores might be needed to surpass the risk of non-representative targeting, which can compromise the procedure and cause the recall. Absolute care should be taken that first 2 - 3 cores were sampled from representative place in the breast, as the bleeding, especialy in loose breasts, can obscure precise targeting in the further course of the procedure.

Only 2.3% of tissue cores floated in formaldechyde solution, which meant that they could be predominantly fatty, hence unrepresentative for analysis. The cores from the lesions containing microcalcifications were not radiographed, as the detection of micro-calcifications in the samples would not be critical for further work-up.

All patients tolerated the procedure well, with only one case of psychosomatic reaction (fainting, dizziness) and 2 patients experiencing moderate local breast pain. No significant complications related to the procedure were recorded. In one patient prolonged venous bleeding occured, treated with consistent compresion of the puncture site for 20 minutes. In one patient local anesthesia was not applied, as the patient informed the staff about severe anaphylactoid reaction 3 years ago, related to lidocaine injection prior to small surgical procedure. The patient agreed that CNB would be performed using only lidocaine skin spray, and experienced moderate but tolerable local pain in the breast.

Our study have some limitations: As the method is not yet generaly accepted in the region as a standard, the indication were set inconsistently in some cases, and the method is done less frequently than necessary because of lack of resources. This is a low-volume study intended primarily to describe the initial experience rather than profoundly examine the value of the procedure, which is already well investigated by many authors. The procedure was performed by three operators with different skill in the technique (1 highly, 2 moderately experienced) which may influence the quality of specimens and the safety.

4. Conclusion

In conclusion, US-guided breast CNB is accurate, safe, and a well tollerable tissue sampling procedure which can be performed only with limited resources, and the results are valuable in the work-up of patients with suspicion of breast malignancy. The operator should adhere to basic interventional US safety standards, and take into account advantages and limitation of the method.

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Scientific Research Publishing

International Journal of Clinical Medicine, 2016, 7, 698-711
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

The Impact of Creative Group Teaching and Educational Booklet Methods on Interpersonal Communications among Midwives in Clinical Setting

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How to cite this paper: Mandana, S., Mohammad, S., Maryam, M., Sadat, H.D.A. and Masud, Y. (2016) The Impact of Creative Group Teaching and Educational Booklet Methods on Interpersonal Communications among Midwives in Clinical Setting. *International Journal of Clinical Medicine*, **7**, 698-711.
http://dx.doi.org/10.4236/ijcm.2016.710076

Received: September 28, 2016
Accepted: October 28, 2016
Published: October 31, 2016

Abstract

Group discussion teaching technique for small groups and encouragement of critical but constructive and creative thinking for finding new and efficient solutions can lead to provision of better health and medical services that is defined in clinical setting, as the clinical psychology finds a way for curing and education. The present study was conducted with the aim to compare the effects of creative group teaching and educational booklet on interpersonal skills of midwives in a clinical setting. The present study was conducted on 97 midwifery graduates working in hospitals in Kerman Province, in two groups of educational booklet (49 midwives) and educational workshop (48 midwives) who participated in a 3-day creative teaching workshop in summer 2015. Creative problem-solving teaching intervention group was taught through educational workshop method, including small group and team working, group discussion and mini lectures. Midwifery 1 intervention group was provided with an educational booklet validated by professors of Nursing and Midwifery School for independent and individual study by midwives working in Kerman Province hospitals. The two groups were matched in terms of personal details. Hospitals were randomly selected, and midwives were selected by quota sampling. Inter-

personal communication skills of both groups were assessed before and after intervention, and two months later using Interpersonal Communication Skills Test. The results obtained were analyzed in SPSS-16 using descriptive statistics, including frequency and percentage, mean and standard deviation, and inferential statistics including U-Mann-Whitney, paired t, independent t, repeated measures ANOVA tests at significance level of $P < 0.05$. Mean changes in interpersonal communication scores in workshop group were significantly greater than those in educational booklet group after intervention, and educational workshop had caused a mean score change of 8.46 in every participant ($P < 0.001$). Two months after educational intervention, mean score change was 8.89 in workshop group, significantly different from 3.11 in educational booklet group ($P < 0.001$). According to paired t-test, mean scores of interpersonal communication significantly increased in both workshop (100.14 to 117.12) ($P < 0.001$) and booklet (96.56 to 99.8) groups ($P < 0.001$). Both teaching methods improved midwives' interpersonal communication skills. Therefore, standardized educational booklets which produce cost-effective similar results are recommended.

Keywords

Education, Interpersonal Communication, Clinical Psychology, Clinical Medicine, Problem-Solving

1. Introduction

Various educational methods, presenting real cases, reflection through debate and exchange of views, and immediate feedbacks will all help improve learning. As an active learning method, practical educational workshops utilize brainstorming, feedback and acquisition of knowledge and skills [1]. Educational workshops are one of the many common ways of transferring information and skills. When participation is poor and participants are not engaged in learning process, and questions and answers, debate and feedback are not provided, the workshop is not actually educational and lectures are wasted. An important point in learning through educational workshop is reflection on new subjects for in-depth learning, which happens in small groups [2]. Hamann *et al.* (2016), in their before/after assessment of an educational workshop on diagnosis and treatment of depression, concluded that the educational workshop provided a practical guide about mental health in a clinical setting [3].

Problem-solving is a cognitive-behavioral process and a coping skill associated with good personal adaptation, and involves five steps: self-concept, problem statement, listing various solutions, choosing the best solution, and testing the chosen solution [4]. Problem-solving, as the basis of care, needs to be addressed and developed [5]. Teaching problem-solving affects people's behaviors and boosts their self-efficacy [6]. Waugh *et al.* (2014) propose that nurses and midwives need training in addition to considering ethical and professional principles before being recruited. In their opinion survey of nurses and midwives, they concluded that at recruitment, seven key skills are necessary

for this profession, one of which is appropriate communication skills [7].

Emergency departments (such as midwifery) are highly complex settings with huge workloads, where tension is high, every second counts, events are unpredictable, and early diagnosis, treatment of patients and correct application of information are commonplace, which requires personnel to have adequate information, and sufficient problem-solving skills for every circumstance [8] [9]. In clinical settings and in dealing with real patients, students learn problem-solving skills, psychomotor ability, communication skills, critical thinking and time management skills, social behavior and self-esteem improvement [10]. Previous studies show that problem-solving training can positively affect critical thinking, self-concept, psychological health, mitigation of depression, and communication [4] [11] [12].

According to Gagne', problem-solving conditions include learner's inner conditions and learning setting, where learner combines simple rules to reach higher rules, and this leads to problem-solving. He therefore considers problem-solving as an essential learning skill, and believes that in problem-solving previous learning, especially rules, should be combined in a new way to create a higher rule [13].

In their workplace, midwives face with unpredictable and stressful events that affect their decision-making. They should therefore learn and apply problem-solving skills in any given situation. In today's complex healthcare, medical teams should be able to act quickly and correctly [14]. Calming the situation and avoiding tension is not only about interaction with patients, but also different aspects of work such as dealing with colleagues. It has been shown that problem-solving skills have a major role in people's dealing with adverse events and life stresses [15]. Shokohee-Yekta also showed that problem-solving training led to improvement in relationships and reduced negative behaviors among people [16].

In view of D'Zurilla and Goldfried, problem-solving stages include: General orientation, problem definition and formulation, generating creative solutions, decision making, and verification [17]. The main task in the third stage (decision making) is preparation of alternative solutions and selection of the most effective one [18]. Brainstorming technique can be used for finding creative solutions. The principle aim is separation of solution production process from evaluation process because production of alternative solutions is often suppressed by evaluation, which prevents creativity. Hence, solutions are not evaluated and judged at this stage [13].

To help mothers, midwives require the right decision making capacity for dealing with problems, and midwives with such a skill can easily deal with challenges in different situations [19]. Gaskell *et al.* (2015) argue that capabilities of midwives can be improved through training in advanced clinical skills, critical thinking, team work, innovative services and problem-solving skills, and thus, strengthening problem-solving skills is also effective in improving care [20]. Ivicek *et al.* (2011) believe that given the complexities of the settings in which medical teams work, where reasoning, decision-making and creativity are required, problem-solving-based training is an appropriate method for coping with these settings [21].

In their systematic review, Choon-Huat Koh (2008) concluded that problem-solving

training positively affected doctors' capabilities after graduation, especially in social and cognitive areas [22]. Based on their mixed method study, McNeill *et al*. (2012) suggested that midwives should have greater involvement in promoting community health, and should be suitably trained to better understand their role in community health [23].

A good physician-patient relationship leads to better patient compliance, and therefore better patient recovery [24]. Thus, the present study was conducted with the aim to compare the effects of problem-solving training through educational workshops and educational booklets on interpersonal communications among graduate midwives in hospital settings based on D'Zurilla model.

2. Materials and Methods

The present quasi-experimental study was conducted on two groups of midwives working in maternity wards of hospitals in the city of Kerman in 2015. Two groups of hospitals were chosen by simple random method as the researcher wrote the names of hospital on small identical pieces of paper, put them in an envelope and drew them one by one. Every other hospital was assigned to intervention 1 or intervention 2 groups, thereby minimizing contact between them. Three hospitals were assigned to intervention 1 and three to intervention 2 groups. Because of the difference in numbers of midwives working in each hospital, midwives were selected per quota from each. To this end, quota was determined by the ratio of midwives per sample size in each group (50 midwives), which provided equal distribution of midwives and produced better quality of work. Once the researcher was sure of the cooperation of the six hospitals, she divided them randomly into two groups. Quota sampling from each hospital was conducted by knowing number of midwives in each and using equation $n = \text{n } N1/\text{N}$, which produced sample size needed from each hospital; where n = sample size needed in each intervention group; N1 = number of midwives working in each hospital; and N = total working population of midwives. The main aim in the present study was to compare mean scores of interpersonal communication in the two groups. Thus, sample size was determined according to comparison of means formula, with 95% confidence interval and 80% test power, where the difference in mean scores between the two groups will be significant when ≥13. Given the range of variations in communication scores of 34 - 170, standard deviation was assumed 26. To overcome potential withdrawals, an extra 6% was added to samples, taking into account ratio of numbers in intervention groups 1 and 2 one-by-one. Hence, final total sample size was determined 100 midwives. Due to similarities in type of intervention with [25] titled "the effect of problem-solving training on decision making in students of medical emergencies, it was also used to determine the sample size. Therefore, according to the appropriate distribution of samples across hospitals, 50 midwives in intervention group 1 and 50 in intervention group 2 participated in the present study (2 midwives withdrew). Permissions were obtained from directors of hospitals and heads of maternity departments, and participants willingly consented to enter the study after they were briefed about study objectives by the

researcher.

The present study was conducted with pretest/posttest design, and participants from both groups were given interpersonal skills questionnaire before intervention. To this end, the researcher introduced herself to the deputy of treatment of Kerman University of Medical Sciences, and explained the study objectives, and obtained permission to enter and sample in hospitals. The researcher then made arrangement to find number of midwives working in hospitals with maternity wards.

Study inclusion criteria were minimum of one year's work experience, not being on obliged services, and not passing life skills workshops such as problem-solving and communication in the past six months. Study exclusion criteria were minimum of two sessions' absence for the intervention group, incomplete questionnaires, withdrawal while completing questionnaires, and failure to study educational booklet.

Data were collected using a two-part questionnaire. The first part consisted of demographic details, including age, education, marital status, employment status, work history, working shift, and history of participation in life skill workshops in the past six months, and the second part assessed interpersonal communications (completed by midwives) using the standard Interpersonal Communication Skills Test, with 34 items based on 5-point Likert scale (almost never, rarely, occasionally, often, and almost always), with scores ranging from 34 to 170. This questionnaire has been used in several studies including [26], and its validity and reliability were confirmed. To determine validity, the original questionnaire was translated into Persian, which was then compared to the original questionnaire by language experts, when initial modifications were made [27]. The questionnaire was the made available to 10 university professors to edit ambiguities in items. The final version was completed by 8 university professors and confirmed with correlation coefficient of 0.75 [28]. After obtaining permission to sample from hospitals, two hospitals did not continue their cooperation due to potential problems associated with participation of their midwives in the educational program. Furthermore, two participants from educational workshop group were excluded due to absence of more than one day from workshop, but educational booklet group remained intact with no withdrawals.

In the first stage and after obtaining permission from the treatment deputy and hospital heads, and ethical consents from midwives, the researcher visited every hospital on different working shifts of midwives (from both groups) and distributed and then collected Interpersonal Skills questionnaires after completion. Intervention was performed in the second stage, and intervention group 2 was called to participate in educational workshop by attending a previously arranged (with university treatment deputy) education venue of one of the intervention hospitals at a previously notified time. Educational workshop intervention was performed over three 4-hour sessions (8am to 12 noon) held in three consecutive days using a variety of teaching methods according to learners' needs. To this end, based on previous studies and related preparatory classes (two private sessions with a psychologist) and acquiring problem-solving knowledge and skills, the researcher prepared educational contents in the form of a Power point

presentation and a pamphlet, which was qualitatively validated by four professors from Tehran School of Nursing and Midwifery; she then held educational sessions according to the contents thus prepared. Educational sessions were conducted by the researcher and supervised by a psychologist through lectures, group discussion, questions and answers, brainstorming, role-play, and critique and debate using D'Zurilla and Goldfried model.

In each session, a summary of the previous session was first presented by participants, followed by teaching new materials through interactive lectures involving participants and two presenters that moderated these sessions and displayed the already prepared Power point part of the educational content for half an hour in each session after conclusions were drawn from discussions. Group members participated in debates and then presented a summary of what they had learned in that session. Issues raised were resolved through questions and answers, and assignments were given for the next session in the form of a clinical scenario similar to experiences described by midwives to review and ponder to find individual solutions and practical strategies, so as to practice creative thinking individually as well as in groups. Timetable of creative problem-solving educational workshop is shown in Table 1.

Additional workshops were held for midwives that were absent for a day for whatever reason. Ultimately, 48 midwives were trained. Problem-solving educational pamphlets were made available to intervention group 2, so that they could be better introduced to educational points.

In intervention group with educational booklet, contents included definitions relating to problem-solving, dealing with problems, creative solutions and their stages and

Table 1. Timetable of creative problem-solving educational plan.

Day	workshop-participants' activities	Duration
One	Free discussion about workplace communication problems encountered with colleagues and patients, and acceptance of the problem as a normal but modifiable phenomenon, and the belief in effectiveness of problem-solving in dealing with problems using small group discussion, performed by group leader and critiqued by other groups.	**2 hours**
	Participants' task: problem statement at the end of group session by group leader. Problem definition and formulation and determination of goals, followed by collection of data and analysis of problem using small group and group discussion, and presentation by group leader, and critique by other groups. Problem analysis by group leader at the end of teamwork session	**2 hours**
	Generating a range of solutions that were critiqued by participating midwives	**2 hours**
Two	**Participants' task:** choice of common problems of clinical midwives group by group leader at the end of sessions, and selection of decision-making solutions and prediction of possible outcomes for each solution. At this stage, consequences and problems associated with implementation of selected solutions and their weaknesses were assessed Finally, decisions and prediction of consequence and weaknesses relating to the selected solution were explained by group leader at the end of each teamwork session.	**2 hours**
	Review of previous sessions and implementation of solutions to real workplace cases proposed by participants through open discussion and role play	**2 hours**
Three	**Participants' task**: choosing the best solution for implementation within the existing context by group leader at the end of group sessions Review and summation of outcomes Evaluation of workshop and opinion survey at the end of teamwork sessions	**2 hours**

effects on problem-solving. Qualitative content validity of the booklet was assessed by five nursing and midwifery professors and necessary modifications were made, and then confirmed by a clinical psychologist. The booklet was then made available to midwives to study and contact the researcher if they had any questions on the number already provided. Intervention ended in the knowledge that study of the booklet had completed in booklet group and creative teaching teamwork sessions had ended in workshop group. Then, the Standard Interpersonal Skills questionnaire was completed by participants immediately after intervention and two months later. Ethical considerations observed included obtaining permission from the ethics committee of Tehran School of Nursing and Midwifery, introductory letter for holding educational workshop from Medical Deputy to hospitals, explanations about study objectives given to participants, and their permission to receive questionnaires, rights to participate or withdraw, ethics permission, registration of study on clinical trials site, and receiving registration code.

One of the study limitations was midwives' shift rotation that made it impossible for all members of intervention group 2 to participate in workshop sessions, so additional sessions were held to overcome this limitation. Another limitation included initial non-cooperation of some hospital heads for facilitating midwives' participation in the teamwork, which was resolved through frequent visits and telephone contacts.

The results obtained were analyzed in SPSS-16, using U-Mann-Whitney, independent t, paired t and repeated measure ANOVA tests.

3. Results

The majority of participating midwives in booklet (42%) and creative problem-solving workshop (39.6%) groups were aged between 31 and 35 years, and also the majority in booklet (68%) and workshop (81.2%) groups were married. The majority of midwives in booklet (94%) and workshop (91.7%) groups had university degree education. Mann-Whitney test showed no significant difference between the two groups. Kolmogorov-Smirnov test confirmed normal distribution of main study variables before intervention and immediately and two months after intervention ($P < 0.05$). Paired t-test was therefore used to verify study hypotheses. Independent t-test showed no significant difference in mean scores of interpersonal communication between booklet (96.56) and workshop (100.14) groups before intervention ($P = 0.64$), but immediately after intervention, interpersonal communication score showed greater increase in workshop (117.12) compared to booklet (99.8) group. According to paired t-test, mean scores of interpersonal communication significantly increased in both workshop (100.14 to 117.12) ($P < 0.001$) and booklet (96.56 to 99.8) groups, with significant differences between before and immediately after intervention scores ($P < 0.001$) (Table 2).

Table 3 shows a significant increase in mean interpersonal communication score from before intervention to two months after in both groups. However, this increase was greater in creative teaching group. On these occasions, mean scores significantly changed in both groups ($P < 0.001$).

Table 2. Mean and standard deviation of scores of interpersonal communication before and immediately after intervention in groups 1 and 2.

Interpersonal communication before and immediately after	Intervention 1 (booklet study)		Intervention 2 (workshop)	
	Before intervention	Immediately after intervention	Before intervention	Immediately after intervention
Mean ± SD	**96.56 ± 11.71**	**99.80 ± 12.40**	**100.14 ± 6.61**	**117.12 ± 10.19**
Paired T-test results	$P < 0.001$ df = 49 t = −408.8		$P < 0.001$ df = 47 t = −808.13	

Table 3. Mean and standard deviation of interpersonal communication scores before and two months after intervention in intervention groups.

Interpersonal communication before and two months after intervention	Intervention 1 (booklet study)		Intervention 2 (workshop)	
	Before intervention	Two months after intervention	Before intervention	Two months after intervention
Mean ± SD	**96.56 ± 11.71**	**99.92 ± 12.43**	**100.14 ± 6.61**	**115.72 ± 10.92**
Paired T-test results	$P < 0.001$ df = 49 t = −627.7		$P < 0.001$ df = 47 t = −110.12	

The results also showed mean change of score in workshop and booklet groups of 8.46 and 3.24 respectively, with a significant difference between them, and significantly greater change in mean score of interpersonal communication in workshop group compared to booklet group. Thus, educational workshop was able to produce a change of score of 8.46 in participating midwives ($P < 0.001$). In the follow-up two months after intervention. Mean score change was 8.89 in workshop group and 3.11 in booklet group, with a significant difference between them. Thus, mean score change in interpersonal communication two months after intervention was significantly greater in intervention groups 2 compared to group 1, and intervention was able to cause mean score change of 8.89 in participants ($P < 0.001$).

Repeated measure ANOVA test showed significant differences in interpersonal communication scores in workshop group before intervention and immediately and two months after intervention ($P = 0.001$) (Table 4). A test criterion of 472.615 was obtained, which confirmed the significant differences in interpersonal communication scores before, immediately after and two months after intervention in workshop group ($P < 0.001$). This was also observed in booklet group ($P < 0.001$).

4. Discussion and Conclusion

The present study showed that teaching midwifery graduates in both educational workshop and educational booklet methods and according to D'Zurilla and Goldfried model positively affected and improved their interpersonal communications. The two groups were matched in terms of personal details before the study. Interpersonal communication score after three days of education was greater in educational workshop group compared to educational booklet group. Although this score also increased in

Table 4. Intra-group effect on interpersonal communication among graduate midwives in groups 1 and 2.

Repeated measure ANOVA	Mean	Standard deviation	Test criterion (F)	Significance
Educational booklet	181.68	2	450.734	$P < 0.001$
Educational workshop	292.81	1.50	472.615	$P < 0.001$

educational booklet group. In a randomized controlled study, Borhani *et al*. taught 25 nurses in a two-day workshop (8 hours per day), and conducted their follow-up over a two-month period through 24 text messages [29]. Their results showed an improvement in ethical sensitivity of nurses after this educational workshop. [30] used educational booklet and VCD to teach cardiac patients before their surgery, and succeeded to resolve their anxiety [31]. [32] studied the relationship between problem-solving and communication skills, and found a correlation between appropriate problem-solving and effective communication skills, which confirmed the fact that learning problem-solving skills per se leads to better interpersonal communications, such that higher problem-solving skill score increases communication score [24] ($P < 0.001$). To improve students' interpersonal communication skills, [33] studied communication method used by teachers, and found that physical activity, happy atmosphere, and respect for students encourage them to learn better and do their homework. When teaching method was changed and students had group exercises, their satisfaction peaked and quality of teaching also improved, which led to a friendlier relationship between teachers and students [34]. In a study by [35], communication skills were taught to general practitioners, which led to improvement in their attitude, confidence in diagnosis, and satisfaction with working relationships [26]. In a study conducted on nursing and midwifery students, [36] found a significant relationship between self-control and self-esteem as factors affecting communications and problem-solving [14]. This study is in agreement with the present study.

The present study showed that the effect of problem-solving skill teaching lasted for two months after intervention, which was in line with Moatari *et al*. study that was conducted to assess the effect of problem-solving skill training on self-concept in nursing students, and the results showed greater improvement in intervention group compared to control group a month after teaching problem-solving skills according to D'Zurilla and Goldfried model (due to time limitations, follow-up was conducted a month after intervention) [10]. In a study (2003) conducted on nursing students by Makoul, a significant difference was observed in communication skills between trained and untrained students, which agreed with the present study results [27].

In contrast to the present study, in Salimi *et al*. study (2011), participation of paramedical students in communication skills workshop made no significant difference in their scores in Interpersonal Skills Test, which may have been due to the difference in participants' academic discipline. Furthermore, participants in their study were students, compared to working midwives in the present study that were in contact with various medical teams, and improvement in their communication skills would give

them greater satisfaction with their profession, which encourages them to improve their behavior; whereas students may regard participation in educational workshop or reading as just another academic unit, and thus not very important. Another factor that affects participants' communication skills is the quality and method of teaching. In the present study, new and varied teaching methods were used in the educational workshop, including group discussion, questions and answers, feedback, reflection, real life scenarios proposed by participants, critique and debate, which may have affected behavior change. These techniques are much more effective than lecture method. However, the relationship between students' interpersonal communication skills and teaching method was not investigated in Salimi et al. study. In the present study, due to their desire for learning problem-solving skills, participants in booklet group scored higher on later occasions due to individual study of educational booklet, which shows the educational effect of individual study.

In a study by Hap (2011), poor verbal communication of nurses after intervention was highlighted that had led to dissatisfaction of service recipients, which disagrees with the present study [30]. Hemati-Maslak-Pak (2014) reported communication skills of ICU nurses favorable, and since ICU nurses deal with patients that are unable to communicate in a normal way, nurses use non-verbal communications for better understanding of patients' needs, which according to Hemati-Maslak-Pak is more effective than physical care. Thus, they have a high communication level [31].

Shahbazi *et al*. (2012) performed problem-solving educational intervention in the trial group in six two-hour sessions over eight weeks according to D'Zurilla and Goldfried social problem-solving model in the form of group discussion, brainstorming, and small group (3 people) debates supervised by two experienced teachers [17]. The results obtained confirmed effectiveness of learning, concluding that problem-solving education improves decision-making [29] and enhances emotional intelligence.

Asuero *et al*. conducted a randomized controlled innovative educational intervention for primary healthcare professionals, and reported post-intervention effect of 0.74, and thus recommended ongoing innovative education for prevention of burnout in these professionals [32]. In the present study, despite slight changes in midwives' interpersonal skills score in the second and third assessments in terms of learning through individual study, the increase in interpersonal skills score immediately after intervention and two months later showed an intervention effect of 1.77. It can be said that deductive or top-down education paradigm has changed. Most learning is now focused on reasoning and roots of the problem and related issues. Although there is still a challenge in the balance between what is taught and learnt or not learnt, learning through problem-solving can help improve people's capabilities [33].

In nursing and midwifery, effective interaction with patients and members of the medical team is essential, and given their career prospects and particular features of these disciplines, their desirable learning method is divergent, through which, a sociably and holistically minded student will use his creativity and initiative in his communications, especially with patients, and offer creative solutions, and thus achieve high

levels of problem-solving [34]. Active and group participation of people in educational programs and their encouragement for critical but constructive and creative thinking in finding solutions will ultimately result in provision of better health services.

Despite the efficacy of educational workshops, problems encountered in holding these workshops in terms of coordination and gathering the personnel (given their huge workload and hospital directors reluctant agreements) to take part in these workshops were the main limitations in the present study.

Thus, despite the positive effects of educational workshops on participants' learning, due to personnel's work and coordination problems for participation in workshops, and also the high costs of holding these workshops; it is recommended that personnel be encouraged to enhance their interpersonal communication skills through content validated educational booklets, which are much more cost-effective and produce nearly the same results. Furthermore, given the importance of communications in medical professions, teaching problem-solving and communication skills to midwifery students can at least be expected to be included in their curriculum as an optional unit. It is further recommended that communication skills education through other globally practiced educational methods such as simulation be studied.

Acknowledgements

The authors wish to thank hospital directors, those in charge of maternity wards, and all midwives for their enthusiastic participation in educational sessions. We also thank the Research Deputy of Tehran University of Medical Sciences, the ethics committee, and Iran's clinical trials center for registration of the present study on their site (code: IRCT201410216284N8). We also thank hospital directors for certifying educational workshops. The present article is the result of a student thesis.

Competing Interests

The authors declare that they have no competing interest.

Authors' Contributions

All of research team participated in study design and coordination and helped to draft the manuscript. Dr. Modarres also collected the data and performed the paper writing. All authors read and approved the final manuscript.

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International Journal of Clinical Medicine, 2016, 7, 712-721
http://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

The Structure and Prevalence of Major Risk Factors of Osteoporosis in Uzbek Women over 50

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How to cite this paper: Ismailov, S.I., Abboskhujaeva, L.S., Alikhanova, N.M. and Allayarova, G.I. (2016) The Structure and Prevalence of Major Risk Factors of Osteoporosis in Uzbek Women over 50. *International Journal of Clinical Medicine*, **7**, 712-721.
http://dx.doi.org/10.4236/ijcm.2016.710077

Received: August 31, 2016
Accepted: October 28, 2016
Published: October 31, 2016

Abstract

Background: Osteoporosis is a systemic metabolic disease of skeleton, characterized by decrease of bone mass and impaired microarchitecture of bone tissue, leading to increased fragility and fractures. Methods: We screened 1855 postmenopausal female, aged from 50 to 80, the residents of Tashkent, Namangan and Qarshi, three cities with the largest populations in Uzbekistan. The duration of postmenopausal period was ≥1 year. Results: The study revealed unequal prevalence of OP with the least in Qarshi (27.3%) compared to Tashkent (33.5%) and Namangan (51.1%). Conclusions: Osteoporosis is common among women at age 50 and over, who live in the cities with largest population in Uzbekistan (Tashkent, Namangan and Qarshi). The risk factors in the studied cohort of women included decrease of body mass, irregular consumption of dairy products and irregular physical activity, history of fractures, and duration of menopause.

Keywords

Menopause, Risk Factors, Osteopenia, Osteoporosis

1. Introduction

Osteoporosis (OP) is the most common disorder of bone metabolism, characterized by decreased bone strength, which leads to increased fracture risk [1]-[4]. The disease affects all age groups and is diagnosed both in women and men. By the prevalence and severity of the manifestations, osteoporosis takes to one of the first places among chronic noncommunicable diseases and becomes an important indicator of public health, as well as in Uzbekistan.

At the present time, there is large number of described fracture risk factors. Thus, the latest edition of the guidelines of US National Osteoporosis Foundation provides 79

conditions, diseases and medications that are associated with increased risk of osteoporosis and fractures, as well as 25 risk factors for falls, and they differ from each other by quality, by strength of evidence, degree of risk and their dependence or independence from bone mineral density (BMD) [5].

Based on data from the National Health and Nutrition Examination Survey III (NHANES III), National Osteoporosis Foundation has estimated that more than 9.9 million Americans have osteoporosis and an additional 43.1 million have low bone density [6] [7]. About one out of every two Caucasian women will experience an osteoporosis-related fracture at some point in her lifetime, as will approximately one in five men [8].

In the majority of postmenopausal women osteoporosis develops insidiously and without symptoms, and appearance of first symptoms indicates on significant loss of bone mass, where the first sign of the disease is usually a fracture. Prevalence of postmenopausal osteoporosis (PMO) is not same in different regions even within same country. Despite the fact that there are standards for detection and early diagnosis of PMO, its prevalence depends on many factors, such as geographic location, climatic conditions, social factors, age, race, etc.

Uzbekistan is the most populous country in Central Asia and due to the fact that its natural and geographical conditions differ from region to region, it becomes challenging to find exact prevalence of PMO.

According to the U.S. Census Bureau International Database (http://www.census.gov/population/international/data), in 2014 the population of Uzbekistan was 29 million people, 17% (4.2 mln) and 3.4% (971,000) of people being ≥50 and ≥70 years of age, respectively. By 2050 in the face of a general population rise to 35 million people, 40% (14 mln) and 12% (4.2 mln) are expected to be ≥50 and ≥70 years of age, respectively. There were no specially designed epidemiological studies concerning osteoporosis and osteoporotic fractures conducted in Uzbekistan. However, according to the Research Institute of Traumatology and Orthopedics, there are at least 30,000 people with osteoporosis and 150,000 with osteopenia in Uzbekistan. The number of patients with osteoporosis and osteopenia is predicted to increase up to 250,000 men by 2020 [9].

The work was initiated to study prevalence and various risk factors of postmenopausal osteoporosis among female residents of Tashkent, Namangan and Qarshi.

2. Patients & Methods

We screened 1855 postmenopausal female residents of Tashkent, Namangan and Qarshi, three cities with the largest populations in Uzbekistan, aged from 50 to 80. The duration of the postmenopausal period was ≥1 year. The groups were comparable by parameters.

2.1. Inclusion Criteria

Duration of osteoporosis and menopause was ≥1 year.

2.2. Exclusion Criteria

Diseases affect bone metabolism, such as hyperparathyroidism, thyrotoxicosis, Cushing's syndrome and disease, hypogonadism in medical history, rheumatic disorders, malabsorption syndrome, renal insufficiency, hepatic dysfunction, and malignancies, as well as prior treatment with medications affecting calcium metabolism 12 months.

2.3. Patients Characteristic

The study was conducted in accordance with the ethical principles stated in Declaration of Helsinki of 1964 (revised in Seoul in 2008). The trail is registered on http://www.who.int/bulletin/archives/79(4)373; http://www.wma.net/en/30publications/10policies/b3/. The study was approved by the Center for the Scientific and Clinical Study of Endocrinology Ethics Committee. Written informed consent was obtained from all participants. A special questionnaire chart was developed in the Center and was filled out for each woman. The chart included demographic and anthropometric data (age, height, weight), gynecological and hormonal history (age of menarche, age of menopause, the number of children, reproductive history), private and familial history of fractures, and the present way of life (physical activity, smoking, drinking, and everyday use of dairy products).

Bone mineral density (BMD) was measured by ultrasound osteodensitometry (Omnisense 8000, Sunlight, Israel). According to clinical guidelines, diagnosis of osteoporosis or osteopenia was based on the values of a T-score, the number of standard deviations (SD) from age norm. Thus, osteoporosis was diagnosed with T-score of ≤−2.5 SD, the parameter's range from −1.0 SD to −2.5 SD determined osteopenia, and the value > −1.0 SD was taken as normal. Every patient filled in a card-questionnaire developed at the Center for the Scientific and Clinical Study of Endocrinology, Uzbekistan Public Health Ministry.

2.4. Statistical Analysis

Results were statistically processed using Excel 2010 and the software package STATISTICA 6.0 (Stat Soft, 2001). Logistic regression was used to calculate OR and 95% CI. Quantitative parameters are presented as M ± (SD), as well as Median (Me) and 25th and 75th percentiles as Inter Quartile Range (IQR). We used the Chi-square test to compare observed data. P values of <0.05 were considered statistically significant.

3. Results

An epidemiological study of1855 postmenopausal women aged ≥50 years (mean age 57.8 (±5.9) years, Me 57.0; IQR 53.0 to 61.0) was carried out within the period from 05.01.2010 to 05.01.2015. The study included women with PMO who lived in Tashkent (n = 963), Namangan (n = 415) and Qarshi (n = 477). Among the examinees, 559 (30.1%) women had normal BMD (nBMD), while osteopenia and osteoporosis were diagnosed in 632 (34.4%) and 664 (35.8%) examinees, respectively (Table 1).

Significantly higher number of women with nBMD belonged to age group 50 - 59

(82.8%; $P < 0.0001$). Aging correlated with progressive decline in the number of women with nBMD: 60 - 69 years-15.6%, 70 - 76 years-1.6%. The number of women at age of 50 - 59 was significantly lower in the group of OP (55.9%) compared to group with nBMD (82.8% OR 0.26; 95% CI 0.20 - 0.34; $P < 0.0001$) and group of osteopenia (66.9% OR 0.63; 95% CI 0.50 - 0.78; $P < 0.0001$). Analysis of dependence of BMD on age revealed the following: the average age of all studied women was 57.8 (±5.9) years, with the age of the residents of Tashkent being slightly higher (59.0 ± 6.4) years) than age of women in Namangan (55.5 ± 5.8) years) and Qarshi (58.2 ± 4.1) years) (Table 2).

Likewise, consistent with this trend, were the results of more comprehensive analysis of the dependence of varying degree of BMD disturbance on age. However, despite the fact that the prevalence of OP was higher in Namangan, the women were 2 - 4 years on average younger than women in Tashkent and Qarshi.

The prevalence of OP depending on the region of residence was studied as the next stage of research. Distribution of women by regions of their residence revealed that significantly less women had normal BMD in Namangan (18.1%) than in Tashkent (30.7%; OR 0.50; 95% CI 0.37 - 0.66; $P < 0.0001$) and Qarshi (39.4%; OR 0.34; 95% 0.25 - 0.46; $P < 0.0001$). In Qarshi, OP is registered less frequently (27.3%) than in Tashkent

Table 1. Characteristics of women in Tashkent, Namangan and Qarshi.

Variable	Tashkent, n = 963		Namangan, n = 415		Qarshi, n = 477		Total, n = 1855	
	n	%	n	%	n	%	n	%
nBMD	296	30.7	75	18.1	188	39.4	559	30.1
Osteopenia	345	35.8	128	30.8	159	33.3	632	34.1
Osteoporosis	322	33.5	212	51.1	130	27.3	664	35.8
			Age					
50 - 59 year	555	57.6	327	78.8	375	78.6	1257	67.8
60 - 69 year	330	34.3	68	16.4	82	17.2	480	25.8
≥70 year	78	8.1	20	4.8	20	4.2	118	6.4
Weight < 57 kg	74	7.7	70	16.8	49	10.3	193	10.4
BMI < 20.0 kg/m^2	15	1.6	11	2.7	26	5.5	52	2.8
Daily consumption of dairy products	208	21.6	90	21.7	235	49.3	533	28.7
Regular physical activity (not less than 30 min per day)	631	65.5	150	36.1	273	57.2	1054	56.8
Cigarette smoking	26	2.7	-	-	-	-	26	1.4
Consumption coffee	52	5.4	41	9.9	-	-	93	5.0
Previous fracture	16	1.7	25	6.0	10	2.1	51	2.7

Note: nBMD—normal bone mineral density.

Table 2. Demographic characteristics of women in Tashkent, Namangan and Qarshi.

Variable	Tashkent, n = 963	Namangan, n = 415	Qarshi, n = 477	Total, n = 1855
Age (year)	59.0 (±6.4)	55.5 (±5.8)	58.2 (±4.9)	58.0 (±6.1)
Me: *IQR*	58.0	54.0	57.0	57.0
	54.0: 63.0	50.0: 59.0	55.0: 59.0	53.0: 61.0
Weight (kg)	75.3 (±13.8)	70.0 (±13.7)	68.0 (±11.3)	72.2 (±13.6)
	74.0	69.0	65.0	70.0
Me: *IQR*	65.4: 84.8	60.0: 78.0	60.0: 75.0	63.0: 80.0
BMI(kg/m^2)	29.7 (±5.3)	28.9 (±5.5)	26.6 (±4.9)	28.7 (±5.4)
Me: *IQR*	29.3	28.3	25.8	28.1
	26.1: 32.9	25.3: 32.3	23.4: 29.1	25.0: 31.9
T-score	−1.86 (±1.5)	−2.34 (±1.5)	−1.52 (±1.9)	−1.83 (±1.7)
Me: *IQR*	−1.89	−2.60	−1.30	−1.89
	−2.91: −0.78	−3.60: −1.20	−2.72: −0.10	−3.0: −0.6
Duration menopause (year)	10.8 (±8.2)	9.5 (±7.2)	9.6 (±6.8)	10.0 (±7.5)
Me: *IQR*	10.0	8.0	7.0;	9.0
	4.0: 16.0	4.0: 14.0	4.0: 12.0	4.0: 14.0

Note: Data presented as mean (±SD); Me—Median; IQR—Inter Quartile Range. -25th and.

(33.4%; OR 0.75; 95% CI 0.59 - 0.95; $P < 0.0001$) and Namangan (51.1%; OR 0.36; 95% CI 0.27 - 0.47; $P < 0.0001$).With age, there is logical growth of women with OP in all regions.

It is known that one of the factors contributing to the development of the OP is a low body weight (less than 57 kg). We have studied the dependence of OP development on critical body weight (<57 kg) and BMI (<20.0 kg/m^2). The number of women with body weight less than 57 kg was higher in the group of OP (14.2%) than in the group of nBMD (11.1%; OR 1.32; 95% CI 0.94 - 1.86; $P = 0.13$), and in the group of osteopenia (5.9%; OR 2.65; 95% CI 1.78 - 3.95; $P < 0.0001$). The share of women with BMI < 20.0 kg/m^2 in the groups with nBMD, osteopenia and OP were comparable and had no significant difference (2.7%, 3.3% and 2.4% correspondingly). A comparative analysis of values by regions of residence has revealed that larger number of women with critical weight resided in Namangan (16.8%) compared to Tashkent (7.7% OR 2.44; 95% CI 1.72 - 3.46; $P = 0.005$) and Qarshi (10.3% OR 1.77; 95% CI 1.20 - 2.62; $P = 0.005$). Among Qarshi residents the BMI < 20.0 kg/m^2 (5.5%) was more frequent than in Tashkent (1.6% OR 3.64; 95% CI 1.91 - 6.95; $P < 0.0001$) and Namangan (2.7% OR 2.12; 95% CI 1.03 - 4.34; $P = 0.05$).

Daily intake of dairy products was another aspect to consider. According to the results of our studies a little over a quarter of the surveyed (28.7%) had constantly in-

cluded in their diet dairy products. It was found that the share of women who consume dairy products on a daily basis was much lower in the group of OP (25.5%) than in the group with nBMD (31.8% OR 0.73; 95% CI 0.57 - 0.94; $P = 0.02$) and with osteopenia (29.4% OR 0.82; 95% CI 0.64 - 1.05; $P = 0.12$). Considering consumption of dairy products in the regional aspect, it should be noted that dairy products were significantly more often consumed in Qarshi (49.3%) than in Tashkent (21.6%; OR 3.52; 95% CI 2.78 - 4.46; $P = 0.0000$) and Namangan (21.7%; OR 3.51; 95% CI 2.61 - 4.71, $P = 0.0000$). Perhaps this explains the lower rate of OP in Qarshi.

An important factor that has an effect on the development of OP is physical inactivity. We have found that the share of physically active women among examinees in the group with OP was much rarer than in the group with normal values of BMD (53.8% vs 60.8%; OR 0.75; 95% CI 0.60 - 0.94; $P = 0.02$). If we consider this factor in the regional aspect, the number of physically active women, among those with OP, in Namangan was significantly lower (26.4%) than in Tashkent (62.4%; OR 0.22; 95% CI 0.15 - 0.32; $P = 0.0000$) and Qarshi (54.6%; OR 0.30; 95% CI 0.19 - 0.47; $P < 0.0001$). In addition, in Namangan, the proportion of physically active women in the OP group is significantly lower compared to the groups with nBMD (49.3%; 95% CI 0.21 - 0.64; $P < 0.0001$) and osteopenia (44.5%; 95% CI: 0.28 - 0.71; $P < 0.0001$)—the difference, which is not observed in other regions.

The share of non-smoking women, among those surveyed, in Namangan and Qarshi comprised 100%, the value which was not high in Tashkent either (2.7%). According to the survey, none of the surveyed Qarshi residents consumed coffee. No significant difference in the occurrence of this factor was seen in Tashkent and Namangan.

In the general cohort of examined women the proportion of those who had previous fractures comprised 2.7%. Low-energy fractures were significantly more often in the history of women with OP (2.9%), compared to women with nBMD 2.5%; OR 1.15; 95% CI 0.57 - 2.31; $P = 0.84$). A separate analysis was carried out regarding previous fractures, as one of the most significant predictors of subsequent fractures, depending on the regions of residence. It was found that women living in Namangan had significantly more frequent fractures in history (6.0%) than women in Tashkent (1.7%; OR 3.79; 95% CI 2.0 - 7.18; $P = 0.0000$) and Qarshi (2.1%; OR 2.99; 95% CI 1.42 - 6.31, $P = 0.005$).

We studied the prevalence of OP dependence on the duration of menopause. Osteoporosis occurs in a far greater proportion of women with menopause that lasts up to 5 years, living in Namangan (31.1%) compared with those of Tashkent (15.3%; OR 2.50; 95% CI 1.49 - 4.19; $P = 0.0007$) and Qarshi (15.8%; OR 2.41; 95% CI 1.33 - 4.36; $P = 0.005$).

There was significantly greater number of women with menopausal duration exceeding 15 years in Tashkent (25.1%) compared with Namangan (18.1% of OR, 1.52; 95% CI 1.14 - 2.03, $P = 0.005$) and Qarshi (13.8% OR 2.09; 95% CI 1.55 - 2.82; $P < 0.00001$). Increase of duration of menopause was associated with progressive decrease of BMD in all regions.

4. Discussion

As is known, female sex and age are the main non-modifiable risk factors of OP in terms of low BMD and fractures. The prevalence of osteoporosis in the female population depends primarily on the age of patients, and may also vary depending on the region of residence. We studied the prevalence of OP risk factors in postmenopausal women, considered in the aspect of their place of residence.

It was found that the average age of women in the study had no statistically significant difference. Nevertheless, despite the fact that the prevalence of OP is higher among women in Namangan, on average, they were 2 - 4 years younger than women of Tashkent and Qarshi. The number of women with OP predictably grows with advanced age, in all studied regions

The reduction of BMD begins at age 45 - 50 years; however, a significant increase in the risk of OP is associated with age 65 and over. Therefore, the age over 65 should be considered a predictor of bone fracture [10].

A recent study on the epidemiology of osteoporosis in the United States found a prevalence of 15.4% among women older than 50 years and a prevalence of 34.9% among women older than 80 years [8]. The prevalence of osteoporosis in Brazil amounted to 8% in women aged 45 - 54 years, 19.2% in women aged 55 - 64 years, and 32.7% in women >65 years of age [11] [12]. The epidemiological studies conducted in Russia demonstrated that osteoporosis affects more than 10 million people in Russia– 30.5% - 33.1% of women and 22.8% - 24.1% of men at age 50 and older, which is consistent with the criteria of the WHO [13]. In the study, conducted in Russia, within the scope of European Study of Vertebral Osteoporosis (EVOS) and European Prospective Osteoporosis Study (EPOS) the frequency of osteoporosis and osteopenia in women, measured in lumbar spine and femoral neck, comprised 34% and 43% correspondingly (by WHO criteria). Analysis of the prevalence of osteoporosis in different age groups demonstrated a distinct trend to its growth in the older age groups of women. During the 5-year prospective follow-up of the sample, the frequency of osteoporosis increased among women up to 40%, which was mainly due to "aging of" sample.The loss of bone mineral density during follow-up, accounted for about 1% per year in both areas of measurement. The most significant losses of bone mineral density of the lumbar spine (3.7%) was observed in the age group 55 - 59 years, of femoral neck (2%) in the group of women, older than 75 years [14].

Weight loss or low body mass index (BMI) are indicators of low bone mineral density (BMI is considered low if <20 kg/m^2, or a body weight less than 57 kg). It also matters if weight loss by more than 10% occurs at age over 25 [10]. According to De Laet, S. *et al.* [15] the negative role of low BMI in fracture risk becomes more obvious if compare it with the associations between osteoporosis and above average BMI. For example, compared with a BMI of 25 kg/m^2, a BMI of 20 kg/m^2 was associated with a nearly two-fold increase in risk ratio (RR = 1.95; 95% CI 1.71 - 2.22) for hip fracture. In contrast, a BMI of 30 kg/m^2, when compared with a BMI of 25 kg/m^2, was associated with only a 17% reduction in hip fracture risk (RR = 0.83; 95% CI 0.69 - 0.99). Authors con-

clude that low BMI confers a risk of substantial importance for all fractures that are largely independent of age and sex, but dependent on BMD. The significance of BMI as a risk factor varies according to the level of BMI. Its validation on international basis permits the use of this risk factor in case-finding strategies.

In our study the numbers of women with body weight less than 57 kg and BMI <20.0 kg/m^2 in the groups with nBMD, osteopenia and OP were comparable and had no significant difference. With regard to regional peculiarities, women with a critical body weight and BMI < 20.0 kg/m^2 are more common among residents of Qarshi.

Physical activity can improve and maintain optimal physiological state of the musculoskeletal system throughout life and slow down the process of age related degradation, observed in people leading sedentary lifestyle [16] [17]. Physically active elderly maintain muscle strength and flexibility, which enables them to cope better with daily household chores. Moreover, regular physical activity reduces the risk of falls and hip fractures in elderly [18]-[20]. Sedentary life-style and immobilization result in rapid bone mass loss associated with accelerated bone resorption and slow bone formation [21]. According to our data, less than half of women in the group with OP lead an active life, with significantly smaller proportion of physically active women in Namangan.

A history of fractures that occur due to minimal injuries-is the most significant risk predictor for subsequent fractures and major clinical diagnostic criteria of OP. Along with this, the primary and main endpoint of any antiosteoporosis therapy is to prevent occurrence of new fractures. In the research, carried out by Saneeva GA *et al.* [22], 45.3% of the patients had a history of low energy fractures of various localizations. In 8.1% of cases fractures occurred repeatedly or had multiple localizations. Atypical for OP fractures of the lower leg or ribs that occurred with minimal impact were registered as "of other localization". The frequency of previous fractures in our cohort of women was low. Concerning regional aspects fractures were more frequent in the history of women, living in Namangan, a history of fractures occur much more frequently than in other regions.

Risk factors for osteoporotic fracture should not be considered to be independent of one another; they are additive and must be considered in the context of baseline age and sex-related risk of fracture. For example, a 55 year old with low BMD is at significantly less risk than a 75 year old with the same low BMD. A person with low BMD and a prior fragility fracture is at considerably more risk than another person with the same low BMD and no fracture [10].

Menopause, as it is and its duration are the most significant risk factor of OP. The onset of menopause is associated with bone mass loss approximating to 2% - 3% a year up till the age of 65 - 70, after which the rate subsequently reduces and equals to 0.3% - 0.5% a year [23].

5. Conclusion

According to acquired results, osteoporosis is quite common among Uzbek women older than 50 years of age (35.8%). Estimation of the prevalence of the disorders of

bone mineral density, depending on the region of residence showed that osteoporosis is significantly more often registered with the residents of Namangan, compared with other regions. Moreover, women affected by osteoporosis in this region are 2 - 4 years younger than their counterparts in Tashkent and Qarshi. Low weight and irregular physical activity, fracture history and duration of menopause are risk factors in the studied groups of women.

Acknowledgements

All the authors contributed equally to the manuscript.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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