

## NURSES' SHORT PERIPHERAL CATHETER FLUSHING: EFFECTIVENESS OF INSTRUCTIONAL GUIDELINES ON KNOWLEDGE AND PRACTICES

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**Background:** Institutional variation in policies and practices related to short peripheral catheter flushing (SPCF) leads to a paucity of knowledge regarding the variables that affect nurses' SPCF practices and their impact on results, which could potentially improve clinical education for nurses, institutional policy initiatives, and patient care. **Aim:** To evaluate the effect of instructional guidelines on nurses' knowledge and practices regarding short peripheral catheter flushing. **Design:** A quasi-experimental (pre/post-test) research design was utilized to conduct the study. **Sample and setting:** A convenient sample of 50 nurses who were working in the Surgical Unit at Menoufia University Hospitals. **Tools:** Two tools were used for data collection involved a structured interviewing questionnaire (tool I) which includes nurses' personal data and knowledge; observational checklist for nurses' practice (tool II). **Results:** The study's findings revealed a very statistically significant positive association between the nurses' total knowledge and total practice scores who were being evaluated before and after the introduction of instructional guidelines for flushing short peripheral catheters. **Conclusion:** It was found that instructional guidelines improved nurses' knowledge and application of brief peripheral catheter flushing. **Recommendations:** Nurses should have access to ongoing educational opportunities and in-service training programs on short peripheral catheter flushing to advance their expertise. **Keywords:** Instructional guidelines, Knowledge and practice, Nurses, Short peripheral catheter flushing

## Introduction:

Insertion and maintenance of short peripheral catheter (SPC) are the nurses most often performed clinical procedure. Even if there are specific recommendations, nurses are responsible for maintaining the cleanliness and functionality of SPCs (O'Grady et al., 2019). Every organization, unit, and nurse have their own unique SPCF policies and care procedures. These disparities have negative consequences for patients, nurses, and medical institutions quality of care (Gonzalez Lopez, et al., 2014 Keogh et al., 2014). Clinical judgement and critical thinking are commonly used terms to characterize nursing processes. Nursing procedures are frequently described in terms of clinical judgment and critical thinking. However, these concepts are insufficient to describe the intricate decision-making skills, information, or abilities that are essential and required to achieve optimal quality of care (Benner, 2018).

In order to get access to the updated knowledge and evidence, the Infusion Nurses Society recommends that all nurses should get training for brief peripheral catheter care at the time of hiring, as well as annually (Gorski, et al., 2016). Although conducting continuous education programs are a guarantee for providing best SPC care and standardize its performance, they are not always implemented. So that, the foundation for the nurses' SPC care practices usually directed by institutional policy or the experiences of the professional nurses in the health care setting (Johansson et al., 2019), which lead to uncertainty and inconsistencies in care practices, especially, when the knowledge is based on outdated evidence. However, there is currently little evidence about SPC care, and the available guidance is inconclusive. Some studies determined that an every-twelve-hour frequency was effective, while others found that a flushing schedule every 24 hours was sufficient to prevent issues. It could be difficult to put the flush volume recommendations into practice (Benner, 2018).

The amount of 0.9% sodium chloride used in clinical settings varies depending on whether prefilled syringes are used, the size of the available syringes (3 mL, 5 mL, or 10 mL), institutional policy, or other factors. According to one study by Campbell, et al., (2019), 3 mL of 0.9% sodium chloride was sufficient to maintain catheter patency. Additionally, a lot of the SPCs research studies that are carried out in clinical settings adherence to designed protocols and procedures or are carried out in laboratories under carefully controlled conditions, which makes it unlikely that they will accurately reflect or translate to the difficult realities of clinical environments (Keogh et al., 2019). Although the policy may specify how catheter sites should be evaluated and flushed, Additionally, nurses consider things like the patient's level of care, vascular health, catheter dwell time, and the kind, frequency, and infusion rates

of any medications or fluids. A nurse frequently chooses the appropriate flushing frequency based on these factors (**Hadaway, 2016**).

The subtlety of short peripheral catheters care, the context in which it takes place, and the limitations of documentation to consider the intricacies of ordinary short peripheral catheters care make it difficult to understand nurses' practices, as is the case with much expert knowledge and expertise (**Wilbanks et al., 2018**). Despite surveys and observations about nurses' care of short peripheral catheters, there is a lack of information about the factors that influence nurses' decisions and the outcomes of these actions. This information could be used to guide clinical education, best practices, and patient care (**Keogh et al., 2017**). The most frequent invasive clinical technique is short peripheral catheter installation, which is frequently done by nurses in hospitals around the world. Short peripheral Each year, more than one billion hospitalized patients have catheters placed. Regular implantation of short peripheral catheters is associated with infections such phlebitis (15.4%), infiltration (23.9%), catheter occlusion (18.8%), inadvertent dislodgement (6.9%), and catheter infection (0.2%) (**Alexandrou, 2014**).

Complications are acknowledged as important contributors to short peripheral catheter failure, which results in the early termination of intravenous therapy, removal of the device, and repositioning of new SPC (**Wallis et al., 2015**). According to one study, there are between 35% and 50% of short peripheral catheters fail. High SPC failure results in treatment interruption, early catheter removal, higher complications, length of hospital stay, expenses, and mortality (**Helm et al., 2015**). One of the primary reasons of SPC failure and poor durability has been recognized as a knowledge and practice deficit on the part of healthcare practitioners (**Keleekai et al., 2016**). Evidence from the past suggests that confidence, practice, and understanding SPC placement are related to success on the first try, and patient problems are decreased when experienced nurses do the procedures. Studies have shown that nurses lack the knowledge and abilities necessary to properly implant small peripheral catheters and address issues including insertion site choice, catheter choice, catheter securement, dwell duration, and treatment complication detection. (**Cicolini et al., 2019**).

#### **Significance of the study:**

Implementing the appropriate educational programs is essential in enhancing nursing practice and enhancing nurses' ability to provide comprehensive patient care (**Aziz et al., 2019**). To enhance nurses' knowledge and skills about SPCs, all of which contribute to improving their satisfaction. At Egypt, there is lack of studies regarding this topic in addition to, by assessing nurses, we found that there is a knowledge deficit and inadequate observed skills which indicated the development of the study. Hence this study aimed to evaluate the effect of instructional guidelines on nurses' knowledge and practices regarding SPCF.

### **Aim of the study:**

The study aimed to evaluate the effect of instructional guidelines on nurses' knowledge and practices regarding SPCF through:

- Assessing nurses' level of knowledge pre- and post- instructional guidelines.
- Assessing nurses' level of practices pre- and post- instructional guidelines.
- Designing and implementing instructional guidelines based on nurses' needs.
- Evaluating the effect of instructional guidelines on nurses' knowledge and practices regarding SPCF.

### **Research hypothesis:**

**H1:** Nurses' knowledge and practices are expected to improve post-receiving instructional guidelines regarding SPCF post-intervention than pre-intervention.

### **Subjects and Method:**

**Research design:** To accomplish the goal of this study (pre/post-test), a quasi-experimental research design was adopted.

**Setting:** This study was carried out in the Surgical Unit at Menoufia University Hospitals, Egypt. These settings were selected because it serves the most populated region and has a high prevalence of patients.

**Subjects:** A convenient sample of all 50 nurses who were working in predetermined settings was enrolled as study participants. Participants who agreed to participate were of both genders, had experienced more than six months, and volunteered to get. While participants who declined to participate, who had a vacation planned, or any debilitating condition (chronic illness, pregnancy, low back pain, etc.) were excluded.

**Data Collection Tools:** Two tools were utilized in the current study, as the following:

**Tool I. A structured interviewing questionnaire:** This sheet was developed by the researcher based on current national and international literature (O'Grady et al., 2019; Piper et al., 2018; Roszell et al., 2016; Keogh et al., 2016; & Goossens et al., 2015), and it contains two parts:

**Part (a):** Nurses' data sheet: It includes 5- items to assess demographic data of the studied nurses as age, gender, qualification, years of experience, and attending training courses about short peripheral catheter flushing.

**Part (b): Nurse's knowledge questionnaire sheet:** It was developed by the researcher based on reviewing the literature (Infusion Nurses Society: Infusion Nursing Standards of Practice, 2016), to assess nurses' knowledge related to short peripheral catheter flushing. It is composed of the following items: definition, the importance, frequency, and type of SPC flushing, reinforcing, and supporting

adherence to current practice recommendations, the complications of short peripheral catheter flushing, and nursing care.

**Scoring system:** Twenty questions were asked in all. There were (40) total points. Less than 50 % (less than 20 degrees) considered to be of poor level. Fair level: those with 50–70% grades (20–28 degrees). A good grade is one with more than 70% (more than 28 degrees).

**Tool II: Nurse`s practice observation checklist sheet:** An observation checklist was developed by the researcher based on reviewing the literature (**Saliba et al., (2020); Vendramim et al., (2020); Ray-Barruel et al., (2020); Infusion Nurses Society: Infusion Nursing Standards of Practice, (2016)**), to assess nurses' practical aspects of the basic competencies related to short peripheral catheter flushing. It consists of the following items: The catheter inserter made his or her selection of the catheter gauge, attachments, pre- and post-medication flushing, short peripheral catheter flushing, and placement based on the requirements of each particular patient. Using a delicate, pulsatile method, cleaning the skin before inserting the needle, rinsing the area before and after giving the medication, and Flushing syringes should be documented to reduce the pressure applied.

**Scoring system:** A total of 100 items on the observation checklist were scored, and each one received one of the following scores: Each correctly completed step receives two points, each mistakenly completed step receives one point, and a step that is not completed receives a zero who achieved less than 60% with adequate practice. If the score was higher than 60%, the practice level was adequate.

**Tool validity and reliability:** Five experts in medical-surgical nursing and medicine evaluated the data collection tool's clarity, comprehensiveness, appropriateness, and relevance as indicators of its validity. In the current study, the internal consistency approach was used to evaluate the two scales' reliability. With Cronbach alpha coefficients for the first tool of 0.97 and the second tool of 0.91, both showed excellent reliability.

**Procedures:** The actual study included three phases:

**A- Preparatory phase:** The researchers examined the contemporary and related literature that was available as textbooks, journals, magazines, and internet searches in order to develop the instruments for data collection and to develop instructional recommendations. After putting the educational ideas into reality, an Arabic handout was created, produced, and disseminated to the study participants.

**Pilot study:** Assessing the tools' applicability, clarity, and estimated time for each, a pilot study including 10% of the nurses from the chosen unit (5 nurses) was conducted. The primary study subjects included nurses who took part in the pilot study.

**Ethical consideration:** A letter from the nursing faculty's dean was used to obtain official approval for the study's conduct. The directors of the aforementioned settings

gave their written approval after being informed of the study's objectives. Before starting the study, the researchers got the nurses' permission and quickly went through its objectives. Additionally, they signed agreements guaranteeing their anonymity and confidentiality and informed the participants that their participation in the study was fully voluntary and that they had the choice to discontinue at any moment, without having to give a reason.

**B- Implementation phase:** The accessible literature, which included books, journals, periodicals, and internet searches were examined by the researchers. The data collection period lasted six months, from the beginning of January 2022 to end of April 2022, and it was finished after the completion of the following stages. The purpose, nature, and anticipated results of the study were explained to the nurses before the interview.

Data collection was started by the researchers by first gathering personal information. After that, each participant's knowledge of short peripheral catheter flushing was evaluated using tool I as a baseline measure, along with their practices of short peripheral catheter flushing using tool II. The results were utilized as a pretest to evaluate how the nurses' performance was affected by the instructions for SPCF.

For patients to understand the study more clearly, the researchers were provided written materials that included illustrations in addition to verbal instructions. The researchers created this illustrative handout based on a review of the relevant literature, the findings and recommendations of earlier research, the opinions of healthcare professionals, and content testing. In five consecutive visits, each patient was scheduled for a minimum of five instruction sessions, each lasting fifteen minutes.

During this phase, instructional guidelines for flushing a SPC were put into practice for 8 weeks. Three sessions have been scheduled for the subject matter (two for theoretical content and two for practice). The nurses who participated in the study were separated into ten groups, and each group's total time was around two hours. Each team had five nurses.

#### **Contents of sessions**

**Session 1:** The session's topics and learning objectives were covered in the introductions given by each researcher. The session was conducted by the researchers in Arabic, which was suitable for the nurse's comprehension. The pretest is where the researchers begin to evaluate nurses' short peripheral catheter flushing knowledge and practices.

**Session 2:** The theoretical portion of the lesson covered knowledge on short peripheral catheter flushing, including its definition, significance, and general information. The data-collecting tools took nurses, on average, about 50 minutes to complete. Photos, movies, posters, and PowerPoint presentations were used to carry it out.

**Session 3:** The theoretical part contained Knowledge about reinforcing and supporting adherence to current practice recommendations, complications, and nursing care of short peripheral catheter flushing.

**Session 4:** Information regarding modern nursing procedures was included in the practical section, which also included a short peripheral catheter flushing. Hand washing, assessment of short peripheral catheter flushing and site, flushing before and after medication administration, catheter gauge, and attachments were all implemented through lectures, posters, and educational films about short peripheral catheter flushing. The inserter selected the attachments based on the needs of each patient.

**Session 5:** With a short peripheral catheter flushing, the practical section provided information on contemporary nursing practices. It was implemented by lectures, posters, and educational films about short peripheral catheter flushing, which included pre-insertion skin cleaning, flushing before and after medication administration, use of a gentle, pulsatile technique, and documentation of flush (medication or fluid chart) syringe to reduce applied pressure.

**C- The Evaluation phase:** The evaluation of research sample knowledge and practice related to short peripheral catheter flushing was carried out one month after the implementation of the instructional guidelines, using the identical format of tools that were used in the pre-test to assess the impact of the instructional guidelines.

**Statistical analysis:** Statistical analysis and data entry were carried out with SPSS for Windows, version 23. For qualitative and quantitative variables, respectively, frequencies and percentages as well as means and standard deviations were used in the data presented. At a P-value of  $< 0.05$ , statistical significance was considered.

### **Results:**

With a mean age of 33.458.7 and 76% female representation, **Table 1** reveals that 46% of the nurses under study were between the ages of 20 and less than 30. In terms of qualification, (44%) of the nurses in the study possess a diploma from a secondary nursing school. Of the nurses who were studied, 46% have less than 10 years of experience.

**Figure (1):** demonstrates that 64% of the nurses who participated in the study stated that they had not gone to a training session on flushing a short peripheral catheter.

**Table (2):** shows that there were highly statistically significant differences between nurses' pre- and post-instruction knowledge of short peripheral catheter flushing ( $P < 0.001$ ).

**Figure (2):** Demonstrates that 20% of the studied nurses had fair knowledge regarding short peripheral catheter flushing pre-instructional guidelines which

improved post-intervention and become 80% of them had good knowledge with highly statistically significant differences pre/post- instructional guidelines.

**Figure (3):** Portrays the nurses' total practice regarding SPCF pre- and post-instructional guidelines and indicated that 33% of the studied nurses had an adequate level of practice pre-instructional guidelines, but post-instructional guidelines it improved and 94% of them had an adequate level of practice.

**Table (3):** Illustrated that there was a highly statistically significant positive relation between total knowledge scores and total practice scores of the studied nurses pre- and post-instructional guidelines implementation regarding SPCF ( $r = 0.81$ ,  $r = 0.43$ ,  $p$ -value  $< 0.000$ ) respectively.

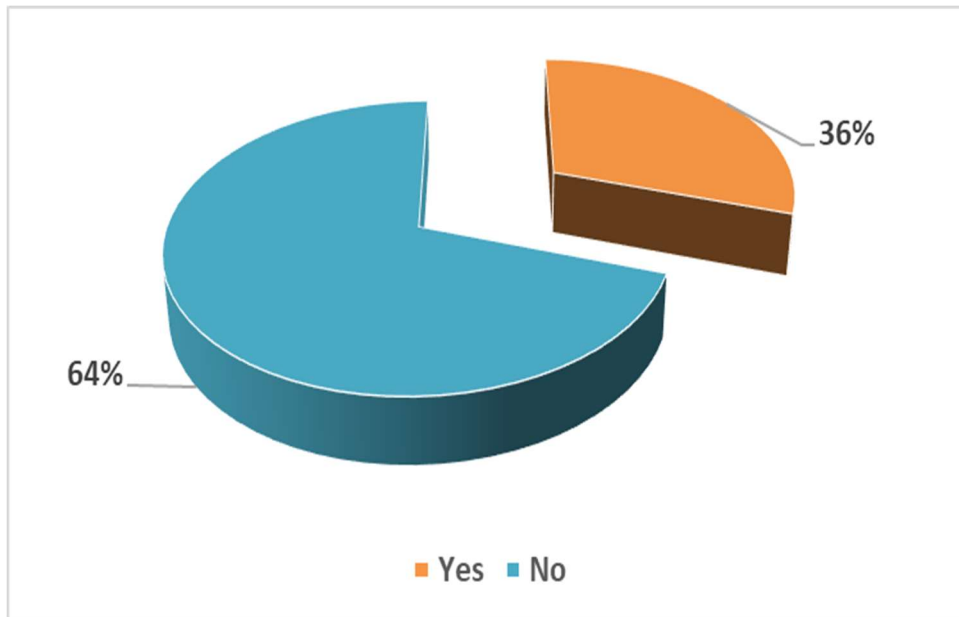
**Table (1): The Studied Nurses' Distribution Concerning Their Demographic Data. (n=50)**

Demographic data:	Studied Nurses	
	N	%
<b>Age:</b> <ul style="list-style-type: none"> <li>▪ 20 &lt; 30</li> <li>▪ 30 &lt; 40</li> <li>▪ ≥40</li> </ul> <p style="text-align: center;"><b>(X±SD): 33.45±8.7</b></p>	23 13 14	46.0 26.0 28.0
<b>Gender:</b> <ul style="list-style-type: none"> <li>▪ Male</li> <li>▪ Female</li> </ul>	12 38	24.0 76.0
<b>Qualification:</b> <ul style="list-style-type: none"> <li>▪ Nursing Diploma.</li> <li>▪ Bachelor of nursing.</li> <li>▪ Master of Nursing.</li> </ul>	22 16 12	44.0 32.0 24.0
<b>Years of experience:</b> <ul style="list-style-type: none"> <li>▪ &lt; 5</li> <li>▪ &lt;10</li> <li>▪ &gt;10</li> </ul>	10 23 17	20.0 46.0 34.0

**X:** Mean

**SD:** Standard deviation





**Figure (1): Percentage Distribution of The Studied Nurses Regarding Their Attended Training Course about Short Peripheral Catheter Flushing. (n=50)**

**Table (2): Comparison between Nurses' Knowledge Regarding Short Peripheral Catheter Flushing Pre- and Post-Instructional Guidelines. (N=50)**

Nurses' Knowledge	Pre-instructional	Post instructional	X <sup>2</sup>	P-value
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	guidelines implementation		guidelines implementation			
	No	%	No	%		
1. Definition of short peripheral catheter flushing	35	70	50	100	132.52	<0.001**
2. Importance of short peripheral catheter flushing	30	60	48	96	142.64	<0.001**
3. frequency and type of short peripheral catheter flushing	29	58	49	98	120.31	<0.001**
4. The complication of short peripheral catheter flushing	24	48	47	94	130.33	<0.001**
5. Nursing care of short peripheral catheter flushing	29	58	49	98	124.56	<0.001**

X<sup>2</sup>: Chi-squared test  
value < 0.001

\*\*; Highly significant at p-

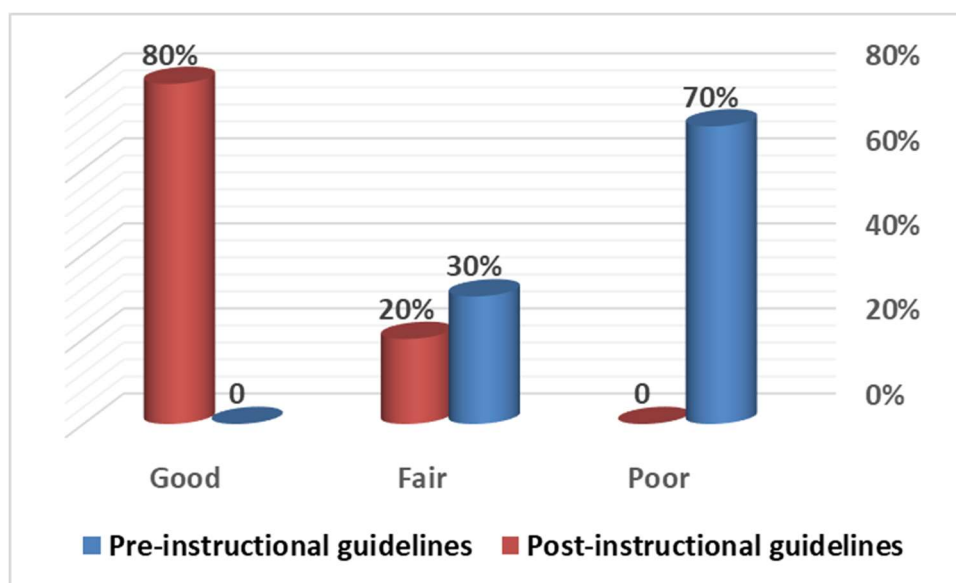
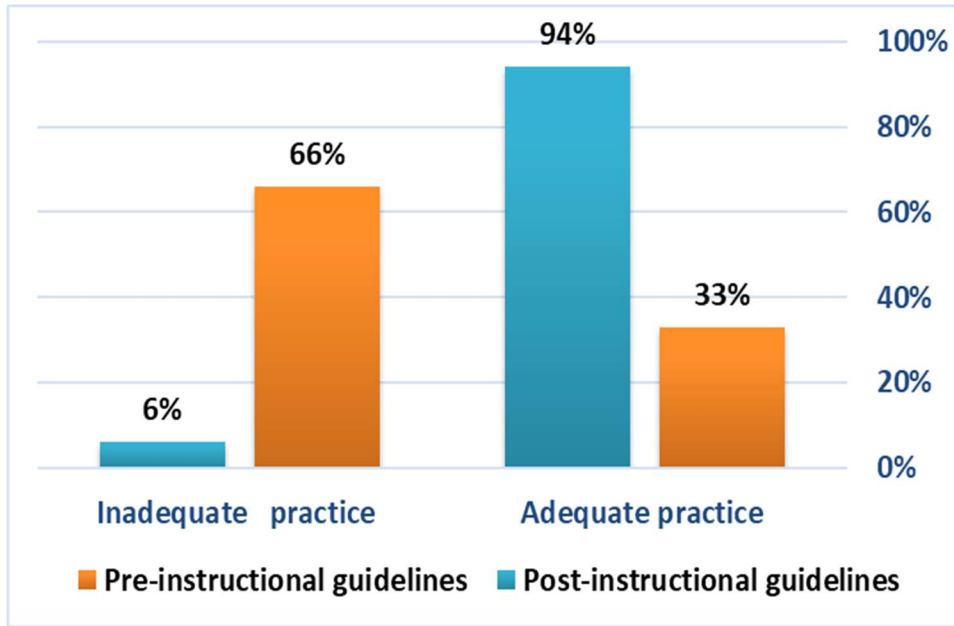


Figure (2): Distribution of Total Level of Nurses' Knowledge Regards Short Peripheral Catheter Flushing Pre-/Post-Instructional Guidelines. (n=50)



**Figure (3): Differences between Nurses' Total Practice Pre- and Post-Instructional Guidelines Regarding Short Peripheral Catheter Flushing. (n=50)**

**Table (3): Correlation between Total Knowledge and Total Practices Pre- and Post-Instructional Guidelines Implementation. (n=50)**

Items	Total Knowledge scores			
	Pre-instructional guidelines implementation		Post instructional guidelines implementation	
	r	p-value	r	p-value
<b>Total Practices scores</b>	0.81	0.000**	0.43	0.003**

**r: Spearman's rank correlation coefficient significant at the < 0.01 level.**

**\*\* Correlation is highly**

### **Discussion:**

According to the study findings, which were published in this article, simplifying procedures and products for short peripheral catheter flushing dramatically decreased the proportion and failure risk, even with relatively low pre-intervention complication rates. It showed that reducing practice variation required increasing public awareness of the value of maintaining vascular access and the methods for doing so, together with goods that make following practice guidelines easier. The usage of pre-filled flush syringes and the instructional intervention received good marks from the nursing staff (**Keogh et al., 2018**).

According to the study's findings, fewer than half of the study nurses have a nursing degree and more than ten years of experience, and half of them are between the ages of 20 and less than 30 years. Bahza (2019) agreed with the study's findings, which showed that the majority of nurses had more than six years of experience. The results of this study show that more than two-thirds of the study's nurses said they had not attended a training session on flushing a short peripheral catheter. This is consistent with **Pancorbo-Hidalgo's (2017)** assertion that professional education and training had an impact on nurses' knowledge. A minority of nurses attend continuing education classes, which is consistent with **Mustafa's (2018)** results and the findings of the current study. From the researchers' perspective, it demonstrated the necessity of implementing instructional guidelines for brief peripheral catheter flushing.

The current study results found that there were highly statistically significant differences between nurses' pre- and post-instruction knowledge of short peripheral catheter flushing. From the researchers' point of view, this reflects the positive effects of guidelines implementation, and the importance and effectiveness of guidelines implementation, which is generally associated with improved knowledge and a better understanding of short peripheral catheter flushing among the studied nurses. The results of the current study showed that one-fifth of the nurses who participated in the study had a good knowledge of the guidelines for short peripheral catheter flushing. From the researchers' point of view, this reflects the need to implement the recommended guidelines.

The results of the current study showed that most of the studied nurses had a good level of knowledge after the instructional guidelines. This improvement demonstrated that the implementation of instructional guidelines was a successful tool for increasing nurses' knowledge. Regarding knowledge about short peripheral catheter flushing, one-fifth of the nurses studied were well aware of the guidelines for

short peripheral catheter flushing. This result can be attributed to the insufficient number of courses related to short peripheral catheter flushing. Most of the nurses noted that they gained knowledge while working with patients. There is also no source for updating and continuing their education. The results are in the same line with **Keleekai et al., (2016)** who studied "Improving nurses' peripheral intravenous catheter insertion knowledge, confidence, and skills using a simulation-based blended learning program" And the results demonstrated a considerable increase in the knowledge scores of the nurses in the intervention group.

The changes, however, consistently revealed a decline in the control group. Studies on short peripheral catheter flushing that was used revealed similar outcomes. Also, **Garner et al., (2018)** conducted a study in India about the "Effectiveness of peripheral intravenous skill continuing education using low-fidelity simulation among nurses" and reported the improvement in knowledge scores post-education. According to research by **Lyons and Kasker (2018)** who studied experienced registered nurses in " Outcomes of a continuing education course on intravenous catheter insertion," the findings of the current study demonstrated that nurses in the intervention group had significantly higher knowledge scores than nurses in the control group following the intervention as compared to before the intervention.

This result agrees with **the previous studies of Keogh et al., (2019); de Sousa et al., (2019) & Keogh et al., (2017)** who stated that the same improvement in the knowledge level among the study group. Similarly, **Ray-Barruel et al., (2019)** studied the " Effectiveness of insertion and maintenance bundles in preventing peripheral intravenous catheter-related complications and bloodstream infection in hospital patients " and **Lavallee et al., (2017)** and reported a significant increase and higher score in the knowledge level .Regarding the investigated practice of nurses regarding short peripheral catheter flushing, the current study showed that there were highly statistically significant differences between the practice of nurses pre and instructional guidelines. From the researchers' point of view, this reflects the positive impact of instructional guidelines on improving nursing practice. This confirmed effective modifications in nursing practice that reflected success in achieving the primary goals of guideline implementation.

The present study shows the general practice of nurses regarding short peripheral catheter flushing before and after instructional guidelines and found that one-fifth of the nurses studied had an adequate level of practice before the educational guidelines, but post-instructional guidelines improved and most of them had an adequate level of practice. From the researchers' point of view, this is reflected in the success of the implementation of instructional guidelines. Results of the study supported by **Morse and McDonald, (2019)** about a straightforward educational program based on posters to increase compliance with **short peripheral catheter**

**flushing** found that nurses' practice on the checklist was much greater just after intervention than it was before intervention.

As a result, the findings of the current study are congruent with those of their investigation. According to a study by **Keleekai et al., (2016)** and observed that the mean practice score of nurses after a simulation-based blended learning program revealed a significant difference compared to before intervention, in the study group. Regarding the study of the relationship between nurses' general knowledge and the general practice of **short peripheral catheter flushing**, the current study showed that there was a high statistical significance of the positive correlation between nurses' general knowledge and general practice before and after instructional guidelines implementation of instructional guidelines. This may be because knowledge is the basis for practice. This reflects the importance of improving nurses' knowledge and practice to help them learn, gain good knowledge, and apply it.

This association is explained by the fact that when nurses have sufficient knowledge that can help them practice well, which is reflected in their patient care. The results of this study supported the aim and hypothesis of the study and confirmed that the knowledge and practice of the nurses studied improved. From the point of view of the researchers, this is reflected in the successful implementation of instructional guidelines and their positive effects. In addition, it reflects the importance and effectiveness of implementing those guidelines for nurses regarding short peripheral catheter flushing that is associated with improved practice. The limitations of the study included repeating the observation. Additionally, it can have an unpredictable effect on the results. So that; the researcher was present during several work shifts to greatly reduce this effect.

**Conclusions:** In this current research findings, concluded that instructional guidelines improved nurses' knowledge and application of short peripheral catheter flushing. There was a highly statistically significant positive relation between total knowledge scores and total practices scores of the studied nurses before and after instructional guidelines implementation regarding short peripheral catheter flushing.

**Recommendations:** The following recommendations are suggested based on the results of the current study: Nurses should have access to ongoing educational opportunities and in-service training programs on short peripheral catheter flushing to advance their expertise. Taught the nurses using the booklet and illustrated pamphlets for each one to improve their information and practices. Replication of the current study with a larger sample of nurses in different settings is required to generalize the results.

**Budget source:** Since they do not receive any additional funding, the researchers are responsible for their expenses.

**Conflict of interest:** That there was no conflict of interest was made clear.

**Ethics approval:** The Nursing Faculty's Institutional Review Board has given its permission.

**Acknowledge:** The department head from the university hospitals and the participants in the study deserve our sincere gratitude and appreciation.

**Author Contributions:** Significant contributions from each researcher were made to the gathering, analysis, and interpretation of the data. GE, IM and AE had full access to all the data and are solely accountable for the accuracy of the data analysis. MS, and ME contributed considerably to the critical editing of the manuscript for essential intellectual content.

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