Original article

How to perform appropriate flushing after lipid emulsion administration using totally implantable venous access devices in long-term total parenteral nutrition and home parenteral nutrition

Naoya Okamura a, Takae Yamato a, Ippei Yamaoka a, Kazuhisa Doi a, Yu Koyama b, *

a Information Center for Infusion Therapy and Product, Otsuka Pharmaceutical Factory, Inc., 115 Kuguhara, Tateiwa, Muya-cho, Naruto, Tokushima 772-8001, Japan
b Department of Nursing, Niigata University Graduate School of Health Sciences, 2-746 Asahimachi, Niigata, Niigata 951-8518, Japan

A R T I C L E   I N F O

Article history:
Received 14 September 2020
Accepted 26 November 2020

Keywords:
TPN
HPN
Lipid emulsion
TIVAD
CV port
Flushing

S U M M A R Y

Background & aims: There has been no clear evidence regarding the appropriate method of flushing catheters and totally implantable venous access devices (TIVADs) after lipid emulsion (LE) administration. Therefore, the aim of the study was to identify appropriate methods of flushing to minimize residual LE when using TIVADs to ensure the safety of long-term total parenteral nutrition (TPN) and home parenteral nutrition (HPN).

Methods: A soybean oil LE containing indocyanine green (ICG) was administered from the injection site of the primary infusion set for flowing TPN, and LE dynamics were evaluated by a fluorescence imaging system. TIVADs were connected to the end of the infusion sets. After LE administration, the tubes and chambers were flushed from the injection site using saline at various speeds (20, 40, 60 mL/min), with and without pulsation. The washout effect of TPN solution after LE administration followed by flushing was examined, as was the washout effect of size differences in the infusion sets.

Results: When the LE was flushed with 20 mL of saline immediately after administering the LE using a standard infusion set (inner diameter 2.5 mm), the LE still remained in the tubes and chambers under any flushing condition. Flushing the LE from the injection site with 10 mL of saline and then flushing >240 mL of TPN solution were effective for minimizing residual LE inside the tubes and chambers. When using an infusion set with a small inner diameter (1.0 mm), the LE inside the tubes and chambers was almost discharged with >20 mL of saline immediately after administering the LE. In all settings, flushing with/without pulsation did not affect LE washout efficacy.

Conclusions: Flushing immediately with saline ≥ 10 mL and then flowing >240 mL of primary PN solution after soybean oil LE administration using the standard infusion set or flushing with 20 mL saline immediately after administering the soybean oil LE using the infusion set with a small inner diameter are effective for minimizing the residual LE in the catheter and TIVAD, ensuring the safety of long-term TPN and HPN.

© 2020 The Author(s). Published by Elsevier Ltd on behalf of European Society for Clinical Nutrition and Metabolism. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Total parenteral nutrition (TPN) is useful for providing almost all nutrients such as amino acids, glucose, lipids, electrolytes, vitamins, and trace elements intravenously, meeting the patient's entire nutritional needs [1]. Because there are many patients who require long-term administration of all nutrients, such as those with chronic intestinal failure due to either benign or malignant diseases, long-term TPN and/or home parenteral nutrition (HPN) is the primary life-saving therapy for such patients [2]. For patients who require long-term TPN (>6 months), including HPN, dedicated central venous access devices (CVADs) for long-term use, such as tunneled CVADs (Hickman, Broviac or Groshong) or totally implantable venous access devices (TIVADs, or another name: CV port), are preferred [2,3]. For the safe and long-term use of CVADs
and/or TIVADs, it is very important to prevent complications, such as accumulated deposits, occlusion of devices, and bloodstream infection; therefore, appropriate management of CVADs and TIVADs is necessary [4]. Catheter flushing is the fundamental and essential procedure for prevention of deposit accumulation and occlusion, which ultimately leads to the prevention of bloodstream infection [5], and it is recommended that sterile 0.9% sodium chloride for injection should be used for flushing [6].

On the other hand, lipid emulsion (LE) is a source of essential fatty acids (EFAs) and energy-dense non-protein calories [7]. Almost all patients should be provided with lipids, particularly if there is no oral intake of fat [3,8]; therefore, intravenous administration of an LE is necessary and preferred for patients receiving TPN, especially long-term TPN and/or HPN. The administration of intravenous LE is commonly divided into 2 methods: using PN admixtures that can be compounded in single bags, dual chamber bags, or three in one/all-in-one (AIO) bags (these contain separate compartments for LE/glucose/amino acids to be opened and mixed before infusion) [2]; or using the LE separately with compounded glucose/amino acids (2-in-1) solutions [9]. AIO bags are generally used around the world, mainly in Europe. Separate use of an LE with 2-in-1 solutions is also popular throughout the world, including the United States of America and Japan, and the LE use may occasionally cause occlusions of the CV route, CVADs, and TIVADs by lipid aggregates, thrombus formation, or the precipitation of drugs or calcium salts [9,10]. Furthermore, residual lipid emulsion in TIVADs has been reported to be a significant risk factor for catheter-related bloodstream infections, because lipids have been identified as a growth factor for microorganisms [11].

As far as we know, there is as yet no clear evidence regarding the appropriate method for soybean oil LE flushing of the CV route and TIVAD. Therefore, we have previously reported briefly on the flushing method after separate administration of the LE [12]. This paper presents the complete results of our investigation of flushing to minimize residual LE when using a TIVAD to ensure the safety of long-term TPN and HPN.

2. Materials and methods

2.1. Preparation for flowing lipid emulsion and TPN

A high-calorie TPN solution, Elneopa-NF No. 2 injection (EP) (1000 mL, Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), was used in the primary infusion set. For tracing soybean oil LE dynamics, indocyanine green (ICG) was used because ICG is easy to uniformly combine with emulsified lipid, and it also has fluorescent characteristics that are useful for later detection, as shown in our past report [12]. The soybean oil LE and ICG mixture, which consisted of Intralipos injection 20% (soybean oil 200 mg/mL, Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) 100 mL with dissolved ICG (Diagnogreen for injection 25 mg, Daiichi Sankyo Company, Ltd., Tokyo, Japan), was also used as an LE in the present study. The shapes and features of the primary infusion sets are shown in Fig. 1. The LEs were administered from the injection sites of the primary infusion sets via the injection site using a secondary infusion set (JY-ND223PL, JMS Co. Ltd. Tokyo, Japan). A 22-gauge Huber-point needle (Huber Plus Non-coring Needle, C.R. Bard, Inc., Murray Hill, NJ, USA) was inserted into the CV port (X-Port isp, C. R. Bard, Inc.), and the other end was connected to a closed connector (Bio- nector S, Vygon Japan Corp., Osaka, Japan). Finally, the prepared LE and EP were given using a common infusion pump at the same flow rate (100 mL/1.2 h).

2.2. Measurement of residual LE using fluorescence imaging

Measurement of residual LE using fluorescence imaging has been described previously [12]. In brief, the distribution of ICG fluorescence in the flushed tubes and chambers was monitored using the IVIS Spectrum live imaging system (PerkinElmer, Boston, MA, USA) with excitation and emission at 745 and 840 nm, respectively. The residual LE in the chamber was calculated by monitoring ICG fluorescence.

2.3. Evaluation of factors affecting the efficacy of flushing the LE

The test model is shown in Fig. 2a. The distribution and amounts of residual LE after flushing with normal saline below the injection site were measured following each of steps 1 to 3.

2.3.1. Step 1. Effect of flushing speed and pattern

Assuming the most difficult case to wash the standard infusion set, JY-NC323RFL (inner diameter 2.5 mm) with dead volume into the injection site was used. The secondary infusion set was removed, and the flow of EP was paused at the same time as the administration of LE was completed, and it was then flushed continuously with normal saline from the injection site at a speed of 20, 40, and 60 mL/min. Both bolus flushing under each condition and pulsatile flushing were performed to determine which flushing pattern would be more effective. For pulsatile flushing, 1 mL of saline flushing at a speed of 60 mL/min was followed by a 1 or 3-s pause.

2.3.2. Step 2. Washing effect of flowing EP after administration of LE

Next, the washing effect of TPN solution was tested using 2 models of TPN administration with saline flushing. The flushing processes are shown in Fig. 2b, and JY-NC323RFL (inner diameter 2.5 mm) was used as the primary infusion set. In model A, after

![Fig. 1. The primary infusion set used for the examination.](Image)
administration of LE, the flow of EP was paused temporarily, and the secondary infusion set was removed. The injection site was then closed, and the flow of EP was restarted. Finally, the residual LE was measured at each point after 80, 240, 420, 660, and 900 mL of EP passed at a speed of 100 mL/1.2 h. On the other hand, in model B, flushing with 10 mL of saline from the injection site was added before restarting EP, and then EP was flowed under the same conditions as model A. After the EP flow is completed, a bolus flush was conducted from the injection site at a rate of 60 mL/min.

2.3.3. Step 3. Effect of route size

In this series of examinations testing the effect of route size, JYNWP861F71 (inner diameter: 1.0 mm), which has a smaller inner diameter and priming volume than the standard infusion set, was used as the primary infusion set. The secondary infusion set was removed, and the flow of EP was paused at the same time as the administration of LE was completed, and it was then flushed immediately with normal saline from the injection site at a speed of 20, 40, and 60 mL/min. Both bolus flushing under each condition and pulsatile flushing were conducted to determine which flushing pattern would be more effective when using a small route size. For pulsatile flushing, 1 mL of saline flush at a speed of 60 mL/min was followed by a pause of 1 or 3 s, the same as Step 1.

2.4. Statistical methods

All experiments were repeated three times, and all values are presented as means ± standard deviation (SD). Differences between the treatments were analyzed using one-way analysis of variance (ANOVA), followed by Tukey’s test when appropriate. The level of statistical significance was set at p < 0.05. Ekuseru Toukei 2015 statistical software (SSRI Co., Ltd., Tokyo, Japan) was used for all statistical analyses.

3. Results

3.1. Effects of flushing speed and pattern

The distribution and amounts of residual LE inside the tubes and chambers after administration of LE followed by saline flushing using the standard primary infusion set are shown in Fig. 3A. ICG fluorescence was strongly detected both inside the tubes and the chambers after flushing with 10 or 20 mL saline, indicating that a large amount of LE remained inside the tubes and chambers (Fig. 3A). The residual amounts of LE inside the chambers did not differ significantly even with different flushing speeds and with pulsatile flushing (Fig. 3B).

In contrast, in model B, adding flushing with 10 mL saline before restarting EP, ICG fluorescence inside the chamber was detected slightly when 240 mL of EP was passed (Fig. 4A a & b). The residual LE inside the dead space of the injection site was not discharged even after 900 mL of EP were passed. Therefore, the amount of LE inside the chamber was increased temporarily after flushing with 10 mL because LE was remaining in the dead space (Fig. 4B).

3.2. Washing effect of flowing EP after administration of LE

The distribution and residual amounts of LE inside the tubes and chambers after flowing EP following models A and B are shown in Fig. 4. In model A, ICG fluorescence inside the tube was not detected when 240 mL of EP was flowed after administration of LE, but ICG fluorescence inside the chamber was still strongly detected (Fig. 4A a & b). The residual LE inside the dead space of the injection site was not discharged even after 900 mL of EP were passed. Therefore, the amount of LE inside the chamber was increased temporarily after flushing with 10 mL because LE was remaining in the dead space (Fig. 4B).
3.3. Effect of route size

The distribution and amounts of residual LE inside the tubes and chambers after administration of LE followed by flushing using the primary infusion set with a small inner diameter are shown in Fig. 5. ICG fluorescence inside the tube was not detected after flushing with 20 mL of saline, and a slight amount of LE remained in the chamber (Fig. 5a). The liquids below the injection site were almost clear using the small inner diameter infusion set compared with the standard infusion set (Fig. 5B). When using the small inner diameter infusion set, the residual amount in the chamber was comparable with bolus flushing, but the higher flushing speed led to less residual amount of LE in the chamber (p < 0.05; one-way ANOVA). When the flushing volume was increased to over 20 mL, the residual amounts of LE did not differ significantly (Fig. 5C).

4. Discussion

Lipid is an essential component of nutrients in the situation of both enteral and parenteral nutrition, and using an LE in parenteral nutrition is helpful for high energy supply, facilitates the prevention of high glucose infusion rates, and is necessary for the supply of essential fatty acids [7,13,14]. Since LE use is preferred for patients receiving PN, especially with long-term TPN and HPN, and colonization of the catheter with subsequent bacterial entry into the catheter lumen has been reported as the cause of 50% of post-insertion catheter-related infections [15,16], it is therefore very important to keep PN devices clean to prevent catheter- or device-related complications to ensure long-term nutritional supply. The appropriate manner of flushing infusion set tubes and TIVADs after LE administration via a secondary infusion set was examined in the present study, because the flushing route of PN after intravenous injection of drugs by the parallel route is fundamental [17], and there was no specific evidence for flushing the LE inside the infusion set and TIVAD thus far. The flushing effect for TIVADs was also examined because there was not enough evidence for their clearance despite their wide use. Though there are several types of chamber shapes, cylindrical, rounded, spherical, and others [18], a cylindrically shaped TIVAD was used in the present study because of its common use. This time a separate type soybean oil LE, not the AIO (three in one/all-in-one) type, was used because AIO products are not available in Japan, and using the separate type LE with
The amount of LE in the chamber is expressed as PPM (parts per million).


adding a cleaned with only a 10-mL saline via the injection site after LE administration, since all LE related complications such as central line infection [22]. Adding a

The Re is under 500 when

Finally, the effect of tube size below the injection site of the primary infusion set on LE washout efficacy in the tube and chamber was examined, and the results showed that, if the primary infusion set with a small inner diameter, which means a narrow lumen, is used, LE washout from the route and chamber could be more effective without pulsation. A possible reason for such results was the higher flow speed in the narrow lumen compared with the standard lumen size. In addition, the Re is over 1000 at a speed of 60 mL/min, and close to 1000 at a speed of 40 mL/min, so that turbulent flow may occur inside the route. This idea supports the result that the LE is effectively discharged when flushed at a high speed of 40 mL/min or more. This result supports the present clinical practice and previous research showing that flushing with 10–20 mL of normal saline using a CV catheter is recommended, but the flushing speed should exceed 40 mL/min using a primary infusion set with a small inner diameter [12,19].

The limitations of the present study are as follows. First, ICG was used to trace the dynamics of emulsified lipids, because some reports have showed that ICG binds to and is incorporated completely and stably into the lipid membrane [23], and has also fluorescence properties in emulsified lipids [24]. However, there is not clear evidence showing that the dynamics of ICG and of emulsified lipids are completely same. A better method for tracing emulsified lipid dynamics would involve using radioisotope-labeled fat in the LE, but it would not be an appropriate method for the safety and health of the researchers. Second, the experiments were performed under ex vivo conditions. However, it would be impossible to detect emulsified lipid dynamics in the route and TIVADs inside patients or healthy volunteers at present. Third, the result was based on the one-load manner, not a repetitive long-term procedure; therefore,

In the present study, the appropriate volume for wash out of LE from tubes and chambers was examined. The dose of saline used for flushing after drug injection is commonly 5–10 mL [5] or 10–20 mL [19], but the present results showed that quite a large amount of LE still remained in both tubes and chambers with flushing volume < 20 mL, and it was also shown that neither flushing speed nor with/without pulsation improved flushing efficacy when a standard infusion set was used. Flushing efficacy of the tube is considered to depend on the strength of the shear force. The Reynolds number (Re) was calculated using the following formula \((\rho V^2 D)/n\), where \(\rho\) is volumetric mass, \(V\) is flow, \(D\) is the internal diameter of the tube tested, and \(n\) is the viscosity of normal saline. The Re is under 500 when flushing speeds are 60 mL/min or less and using a standard infusion set as the primary infusion set, so turbulent flow did not occur under any conditions in the present study [20]. Therefore, the shear force did not differ significantly.

Then, the flush timing and the effect of primary TPN flow after LE administration were examined, because LE will generally be administered in parallel during TPN in the clinical setting. The results showed that immediate flushing by 10 mL of saline followed by LE administration was more effective for washout of LE inside the tubes and chambers if TPN volume was ≥ 240 mL compared with no flushing after LE administration. A considerable amount of LE still remained at the injection site having dead space if immediate flushing was not performed, because the liquid does not flow in the dead space [21]. Therefore, we recommend immediate flushing with 10 mL of saline via the injection site after LE administration, since all LE inside the dead space and most LE (>95%) inside the tube were cleaned with only a 10-mL saline flush, leading to reduced catheter-related complications such as central line infection [22]. Adding a final flush and rocking properly after completing TPN administration could minimize the residual amount of LE, as well as of TPN solution, in the chamber to reduce the risk of infection. The effect of TPN flow speed on LE washout efficacy at the chamber was also checked, and the result showed that TPN flow speed did not affect LE washout efficacy, and TPN flow volume was a main factor related to LE washout efficacy (as shown in Supplemental data 1). Whether the composition of the infusion solution affected LE washout efficacy was also considered, because TPN containing fat-soluble vitamins includes surfactants that are also compatible with lipids, but if a PPN solution including no surfactants was used, LE washout efficacy at the chamber was comparable to that of TPN (as shown in Supplemental data 2).

Typical fluorescence imaging images of tubes (a) and chamber (b) after a bolus flush at 60 mL/min immediately after administration of LE using a small diameter infusion set. B. Appearance of the liquid below the injection site after a 20-mL bolus flush at a rate of 60 mL/min immediately after LE administration. When using JY-NC323RFL (a) or JY-NWP95L1FT (b) as the primary set, and water (c). C. Residual amounts of LE in the chamber after flushing under each condition using a small-diameter infusion set The residual amount of LE in the chamber is expressed as PPM (parts per million).

**Fig. 5.** A. Typical fluorescence imaging images of tubes (a) and chamber (b) after a bolus flush at 60 mL/min immediately after administration of LE using a small diameter infusion set. B. Appearance of the liquid below the injection site after a 20-mL bolus flush at a rate of 60 mL/min immediately after LE administration. When using JY-NC323RFL (a) or JY-NWP95L1FT (b) as the primary set, and water (c). C. Residual amounts of LE in the chamber after flushing under each condition using a small-diameter infusion set The residual amount of LE in the chamber is expressed as PPM (parts per million).
the present study does not necessarily represent the emulsified lipid washout effects with long-term or repetitive LE administration. Long-term or repetitive LE administration may cause accumulation of fat in the route and chamber due to aggregation of small amounts from daily LE administration; therefore, we believe that proper daily management of the TPN route and TIVAD will reduce catheter-related complications, such as deposit accumulation, occlusion, and bloodstream infection, and maintain the safety of long-term TPN and HPN. Fourth, we examined the flushing dynamics of only soybean oil LE in the present study, therefore, our results do not always apply to other LEs (e.g., olive oil, fish oil, etc.). Further research on flushing dynamics is desired for other types of LE in the future.

5. Conclusion

Flushing with ≥10 mL of saline immediately, followed by > 240 mL of primary PN solution after soybean oil LE administration using the standard infusion set or flushing with ≥20 mL of saline immediately after administering soybean oil LE using an infusion set with a small inner diameter is effective for minimizing the residual LE in the catheter and TIVAD to ensure the safety of long-term TPN and HPN.

Statement of authorship

YK and TY designed the research; TY, IV, and KD conducted the research; NO collected the data; NO and YK analyzed the data; TY summarized the data; NO and YK wrote the manuscript and YK had primary responsibility for the final content. All authors read, checked, and approved the final manuscript.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None declared, except that NO, TY, IV, and KD are employed by Otsuka Pharmaceutical Factory, Inc.

Acknowledgments

The authors would like to thank Mr. Hiroshi Iwakiri at Otsuka Pharmaceutical Factory, Inc. For his helpful advice regarding research planning, and Mrs. Hansani Madushika Abeywickrama at Niigata University Graduate School of Health Sciences for her excellent advice on data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2020.11.019.

References