ORIGINAL ARTICLE

Influence of polyvinyl chloride infusion extension tube on propofol injection pain

A randomised controlled study

Qi Wu, Na Zhang, Yong Shen, Yufei Jia and Weifu Lei

BACKGROUND Propofol injection pain is a common and unsolved anaesthesia problem.

OBJECTIVES The present study attempted to confirm that the plasticiser di(2-ethylhexyl) phthalate in polyvinyl chloride (PVC) infusion tubes may increase propofol injection pain by increasing the aqueous propofol concentration.

DESIGN A randomised controlled study.

SETTING University teaching hospital, 1 April to 25 June 2013.

PATIENTS One hundred patients scheduled for elective surgery were allocated randomly to the PVC or the control (C) group. The PVC group received a propofol (Diprivan) infusion via a 1-m PVC infusion extension tube, whereas group C received propofol injected directly through the port of the cannula.

INTERVENTION After the syringe was loaded with propofol, air was expelled from the tube and the syringe was left standing for 5 min; intravenous propofol $0.5\,\mathrm{mg\,kg^{-1}}$ was then injected either through the PVC tube or directly into the cannula.

MAIN OUTCOME MEASURE A verbal rating scale was used to evaluate the propofol injection pain in both groups.

Di(2-ethylhexyl) phthalate and aqueous propofol concentrations were also measured in samples of propofol after simulated injection. To investigate whether the increase in aqueous propofol concentration was caused by leached di(2-ethylhexyl) phthalate, the same amount of di(2-ethyl-hexyl) phthalate as that measured in the PVC group was added to the samples (group D).

RESULTS The incidences of pain in groups PVC and C were 88 and 46%, respectively ($P < 0.0001$). The di(2-ethylhexyl) phthalate concentration in group PVC ($1.01 \pm 0.07\,\mathrm{\mu g\,ml^{-1}}$) was greater than that in group C (lower than the detection limit of $0.03\,\mathrm{\mu g\,ml^{-1}}$). No significant difference was found between the aqueous propofol concentrations in groups PVC ($25.9 \pm 1.8\,\mathrm{\mu g\,ml^{-1}}$) and D ($24.4 \pm 1.1\,\mathrm{\mu g\,ml^{-1}}$) ($P = 0.22$), which were significantly higher than that in group C ($14.3 \pm 1.0\,\mathrm{\mu g\,ml^{-1}}$) ($P = 0.079$).

CONCLUSION Propofol injection pain is increased by contact with PVC infusion tubing as a result of an increase in aqueous propofol concentration caused by di(2-ethylhexyl) phthalate leaching into the lipid emulsion.

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Introduction

Propofol is highly soluble in fat and insoluble in water. Currently, the propofol injection preparation used clinically is a lipid emulsion. It has been reported in the literature that the incidence of propofol injection pain in adults is 28 to 90%.[1] The incidence of propofol injection pain is ranked third among 33 common anaesthesia problems in outpatient procedures and is ranked seventh among the 33 major clinical concerns.[2,3] To date, most studies have concluded that the intensity of propofol injection pain is positively correlated with the aqueous free propofol concentration in the lipid emulsion.[4–6]

Target-controlled infusion (TCI) is a common method of administration of propofol.[7,8] In this technique, a syringe

From the Department of Anaesthesiology, Qilu Hospital of Shandong University (QW, NZ, WL), Shandong Quality Inspection Centre for Medical Devices, Jinan, China (YS, YJ)

Correspondence to Weifu Lei, Anaesthesiology Department, Qilu Hospital of Shandong University, 107 WenhuaXi Road, Jinan, China
Tel: +86 531 82166460; fax: +86 531 82168257; e-mail: leiweifu@163.com; 915188774@qq.com

pump incorporating a microcomputer is employed to calculate and implement the injection strategy. It is designed, on average, to maintain the drug concentration in blood at the target level. The induction bolus dose must be administered by the TCI pump; otherwise, the pump cannot correctly predict the blood concentration. Because there is some distance between the pump and the infusion cannula, it is necessary to connect the pump to the patient using an infusion extension tube. At present, extension tubes are manufactured from polyvinyl chloride (PVC). PVC contains a high content of plasticiser, the most common being di(2-ethylhexyl) phthalate (DEHP). Some studies have shown that lipid emulsion can leach DEHP out of the tubing,[9–12] and others have shown that plasticisers can accelerate the release of drugs in emulsion microspheres.[13,14] Therefore, we suspected that PVC tubes might increase the aqueous free propofol concentration because of the presence of leached plasticiser, and further increase the incidence and intensity of propofol injection pain.

The aims of the present study were to establish whether the use of a PVC infusion tube would increase pain on injection of propofol and, if so, whether the mechanism was that DEHP in PVC materials leaches out and increases the aqueous propofol concentration.

Methods
Ethics committee approval for the study (Ethical Committee 12176) was provided by the ethics committee of Qilu Hospital of Shandong University, Jinan, China (Chairperson Professor Xiao Yang Chen) on 8 November 2012 and informed written consent was obtained from all patients. The study was conducted in Qilu Hospital of Shandong University, a university teaching hospital. One hundred and five patients [aged 18 to 65 years, American Society of Anesthesiologists' (ASA) physical status 1–2 and BMI $\leq 35\,\mathrm{kg\,m^{-2}}$] scheduled for either urological or general surgery were enrolled in this single centre, double-blind, randomised controlled trial between 1 April and 25 June 2013.

Exclusion criteria were peripheral vascular disease, chronic pain syndrome, recently administered analgesic or sedative drugs, a psychiatric history, a history of upper limb trauma or severe cardiovascular disease.

Patients did not receive premedication. Monitoring in the operating theatre included ECG, heart rate, pulse oximetry and non-invasive arterial blood pressure measurement. A 20-gauge cannula (Becton Dickinson, S.A. Fraga, Spain) was inserted into a vein on the dorsum of the hand and attached to an infusion of Ringer's solution running at a rate of $10\,\mathrm{ml\,min^{-1}}$. Propofol (Diprivan serial numberX11211B; AstraZeneca, Cheshire, UK) sealed in a 20-ml glass ampoule was drawn into a 20-ml polypropylene syringe (Becton Dickinson, S.A. Fraga, Spain). The plunger of the syringe was rubber free to

prevent contamination with plasticiser from this source. Patients were assigned randomly to the PVC group, which received propofol via a PVC infusion extension tube, or to the control group C, in which propofol was injected directly into the injection port of an intravenous cannula. The randomisation was undertaken by the statistician using a computer-generated random number table (SAS version 7.0.1). For each patient, the number and intervention allocation were kept in opaque, sealed envelopes. When the study began, the envelope was opened by a research nurse who did not participate in pain assessment. She then prepared the injection under a piece of cloth. Thus, the patients and assessor were blinded to treatment allocation. In group PVC, the proximal end of a PVC infusion extension tube of 1 m in length and 1.3-mm inner diameter (Sujia, Jiaxing, China) was connected to the syringe, and the distal end through a 22-gauge needle to a 20-gauge intravenous cannula; a small volume of propofol in the syringe was ejected to expel the air in the syringe, the extension tube and the cannula. In group C, the syringe was connected directly through a 22-gauge needle to the injection port of a 20-gauge intravenous cannula; a small volume of propofol in the syringe was ejected to expel the air in the syringe and the cannula. The materials in contact with propofol in each group are shown in Fig. 1.

The equipment was left to stand for 5 min before propofol was injected. The standing time was determined arbitrarily in order to simulate the contact time of the infusion tube with propofol in routine TCI anaesthesia procedures. The research nurse then injected propofol $0.5\,\mathrm{mg\,kg^{-1}}$ at a rate of $0.5\,\mathrm{ml\,s^{-1}}$, either through the PVC tubing or directly into the injection port of the intravenous cannula. This slow rate of delivery of propofol was used to ensure that patients retained consciousness during pain assessment. A stopwatch was used to control the injection speed.

Pain on injection was assessed by an assessor using a four-point verbal rating scale (VRS): 0 = no pain, 1 = mild pain (pain reported only in response to questioning without any behavioural signs), 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning), or 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears). The assessor first observed the patients' reaction to assess scores of 2 or 3; if there was no explicit response, the assessor asked patients 2 min after the injection to provide scores of 0 or 1. This VRS method had already been used in other studies that evaluated propofol injection pain.[15–17] The occurrence of pain was defined as any patient with a VRS greater than 0. When the clinical trial was finished, anaesthesia was induced by administration of propofol $1.5\,\mathrm{mg\,kg^{-1}}$, fentanyl $5\,\mathrm{\mu g\,kg^{-1}}$, and vecuronium $0.1\,\mathrm{mg\,kg^{-1}}$.

Fig. 1
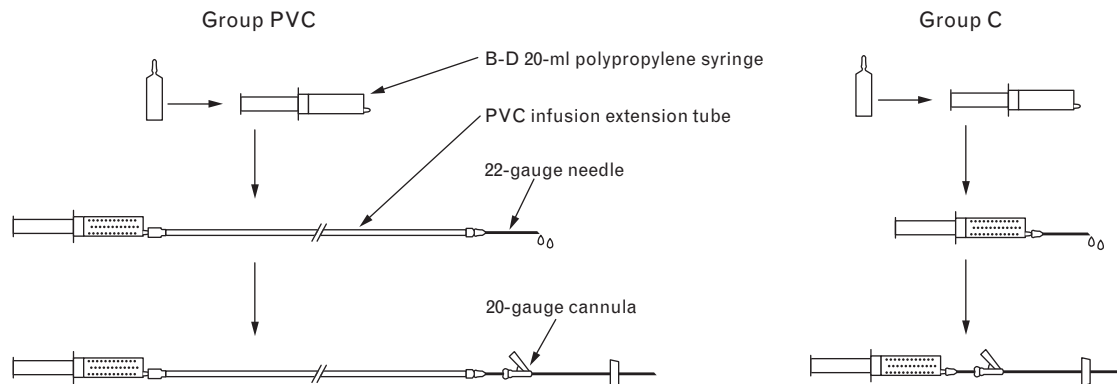
Administration of propofol in the polyvinyl chloride (PVC) group via a PVC infusion extension tube. In control group (C), the syringe was connected directly through a 22-gauge needle to a 20-gauge cannula.

Measurement of di(2-ethylhexyl) phthalate content in propofol

We measured the DEHP content in propofol in five samples from each method of administration. The equipment was prepared in the same way as for the clinical trial, but propofol was injected into test tubes instead of into patients. Each syringe and extension tube was used only once. One-millilitre samples were vacuum dried at $50°C$, and then dissolved in 1 ml of n-hexane and Vortex and filtered by a $0.45 \mu m$ membrane.

The purity of the DEHP standard (Wako Chemicals, Neuss, Germany) is 99.7%. The measurement equipment used was an Agilent 7890A-5975C gas chromatograph-mass spectrometer. The temperature of the injection port was $280°C$; the column temperature was maintained at $150°C$ for 0.5 min, then heated at a rate of $20°C min^{-1}$ until a temperature of $280°C$ was achieved and then maintained for 7 min. The carrier gas was helium, at a flow rate of $1.5 ml min^{-1}$; the ion source was electron ionisation.[11]

Measurement of the aqueous free propofol concentration

We measured aqueous free propofol concentration in five samples from each method of administration. The samples were prepared by simulated injection in the same manner as in the clinical trial. We assumed that the average patient weighed 60 kg. The injection volume was $0.5 mg kg^{-1}$, as in the clinical trial. Consequently, a 3-ml (30 mg) sample was collected after each simulated injection. Because the requirement of the dialysis process was for a 20-ml sample, seven 3-ml samples were collected and 1 ml was discarded. Thirty-five simulated injections were performed in the PVC and control (C) groups, resulting in five 20-ml pooled samples for dialysis

from each group. Each syringe and extension tube was used only once in the simulated injections.

In order to verify whether the main reason for the increase of aqueous propofol concentration was DEHP, a new group D (DEHP added artificially) was created. In this group, the same amount of DEHP ($1.01 \mu g ml^{-1}$) as that measured in group PVC was added to propofol to prepare five samples.

The aqueous free propofol concentrations in groups PVC, C, and D were measured. Dialysis tubes with a cut-off molecular weight of 3500 to 4000 Da (Union Carbide, Piscataway, New Jersey, USA) were filled with 2.5% (w/v) glycerol, bent at the ends, bound and then placed into the samples in a beaker for 24 h at $25 \pm 1°C$. The dialysis tubes were then removed. The propofol concentration in glycerol was measured as the aqueous free propofol concentration.[4,18]

The purity of the propofol standard substance (Zhongke Taidou Chemical Co., Ltd., Jinan, China) is 99.41%. The measurement equipment used was a Waters 2695 high performance liquid chromatograph with a 2996 diode array detector. The detection ultraviolet wavelength was 271 nm, the mobile phase was methanol:water:formic acid 85 : 14 : 1, flow rate was $1 ml min^{-1}$, the column (stationary phase) was C18 $5 \mu m$, length 250 mm, diameter 4.6 mm (Dikma Technologies Inc., Lake Forest, California, USA), the column temperature was $25°C$, the pH was 3.0 and injection volume was $10 \mu l$.[18]

Measurement of di(2-ethylhexyl) phthalate content in infusion extension tube and syringe

The DEHP content in the infusion extension tube, syringe body and piston were measured by Hangzhou CIRS Co. Ltd (Hangzhou, China) according to EU

standard EN 14372:2004 method, using gas chromatography-mass spectrometry for quantitative analysis.[19]

Power analysis

The study hypothesis was that a PVC infusion extension tube could aggravate propofol-induced pain. The primary outcome was the difference in the pain incidence between the groups. The secondary outcomes were the differences in pain intensity between the groups. On the basis of published data,[1] we hypothesised that the incidence of propofol-induced pain in the PVC group and C group would be 80 and 50%, respectively. Fifty patients per group were calculated to suffice for a power of 89% and a level of significance of 5%.

Statistical analysis

The Kolmogorov–Smirnov test was used to check normal distribution of patients' ages and weights, DEHP

concentrations in propofol and aqueous free propofol concentrations. The difference in the incidences of pain between groups was evaluated using the χ^2 test. The difference in pain intensity between groups was evaluated using the Mann–Whitney U-test. Comparison of aqueous free propofol concentrations was performed using the Mann–Whitney non-parametric test due to the small sample size. P values < 0.05 were considered statistically significant. Data were analysed using SPSS version 19.0.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Of the 105 patients, five refused to participate in the study (Fig. 2). Patients' ages and body weights followed a normal distribution and did not differ between groups (Table 1). The number of patients who reported pain because of propofol administration, and the VRS scores,

Fig. 2
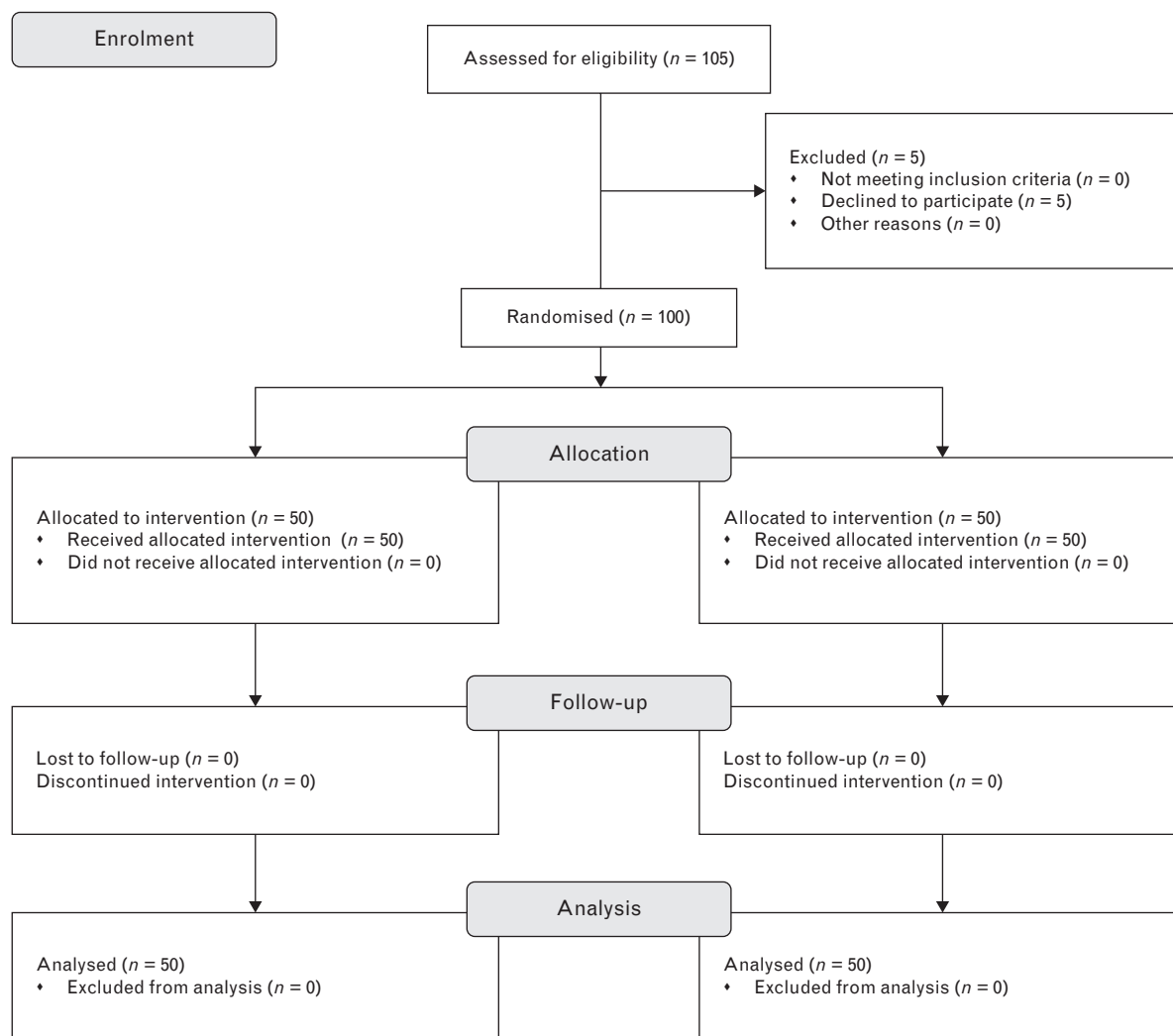
Study flow diagram.

Table 1 Patients' gender, age and body weight in the polyvinyl chloride and control groups

	Men/women	Age (years)	Weight (kg)
PVC group	29/21	53 ± 12.8	64 ± 10.6
C group	27/23	53 ± 13.5	66 ± 11.5

Values are patient numbers (men/women) or mean ± SD. C, control; PVC, polyvinyl chloride.

differed significantly between the two groups ($P < 0.0001$ and $P < 0.001$, respectively) (Table 2).

The DEHP concentration in propofol followed a normal distribution in group PVC and was $1.01 \pm 0.067 \, \mu g \, ml^{-1}$ (95% confidence interval, CI 0.93 to 1.09); in group C, the concentration was less than the lower detection limit of $0.03 \, \mu g \, ml^{-1}$. The aqueous free propofol concentrations in groups C, PVC and D followed a normal distribution and were $14.3 \pm 1.0 \, \mu g \, ml^{-1}$ (95% CI 13.1 to 15.6), $25.9 \pm 1.8 \, \mu g \, ml^{-1}$ (95% CI 23.7 to 28.1) and $24.4 \pm 1.1 \, \mu g \, ml^{-1}$ (95% CI 23.0 to 25.8), respectively. Group C differed significantly from groups PVC and D (both $P = 0.0079$). Groups PVC and D did not differ ($P = 0.22$). The DEHP content in the infusion extension tube was $170 \, mg \, g^{-1}$, whereas the DEHP content in the body and piston of the syringe was less than the lower detection limit of $0.01 \, mg \, g^{-1}$.

Discussion

The present study demonstrated that propofol lipid emulsion can cause significant increases in the incidence and intensity of propofol injection pain. The main reason for this is that the plasticiser DEHP from PVC infusion extension tubes can leach into propofol, and then increase the aqueous concentration of propofol.

Pain at the injection site during induction of anaesthesia with intravenous propofol is very common, resulting in an unpleasant experience for patients, and is sometimes severe enough to cause evasive actions such as hand retraction. Currently, the propofol lipid emulsion Diprivan, which is commonly used in clinical settings, is an oil-in-water emulsion, in which most propofol molecules are dissolved and dispersed in the oil phase. However, there is still a small proportion of free propofol molecules

Table 2 The numbers and percentage of patients who reported pain during propofol infusion in the polyvinyl chloride and control groups

	PVC group ($n = 50$)	C group ($n = 50$)
Patients complaining of pain	44*	23*
Incidence of pain (%)	88%	46%
None	6	27
Mild	12	12
Moderate	21	9
Severe	11	2
VRS of pain	2 (0 to 3)#	0 (0 to 3)#

Data are presented as n, proportion or median (range). VRS, verbal rating scale. *$P < 0.0001$ between groups. #$P < 0.001$ between groups.

in the aqueous phase. These free propofol molecules can cause injection pain by directly or indirectly stimulating the vessel wall. The instant pain caused by propofol injection is because of the free propofol molecules directly stimulating venous nociceptive receptors or free nerve endings, which then transmit nerve impulses through Aδ fibre centres, thereby causing pain.[20] The delayed pain caused by propofol injection is because the stimulating substances come into contact with the vascular endothelium and stimulate the kallikrein–kinin system to generate bradykinin, causing local vasodilatation and increased permeability, thereby further exposing nerve endings to free propofol molecules in the aqueous phase.[20] Free propofol in the aqueous phase is the cause of injection pain, and the incidence of propofol injection pain is positively correlated to the aqueous free propofol concentration; this conclusion has already been accepted by most scholars.[4–6]

In TCI anaesthesia, an infusion extension tube is necessary to connect the syringe pump to the cannula. Currently, the material of most medical infusion extension tubes is PVC. Pure PVC has poor flexibility and the addition of a plasticiser is required, most commonly DEHP. The mechanism of action of DEHP is to form non-covalent bonds with PVC molecules to form a solid solution in which PVC molecules can slide across each other, increasing the flexibility of PVC. DEHP is highly lipophilic. Consequently, DEHP in infusion tubes can be leached into propofol easily during infusion.[9–12] DEHP is a potential carcinogen, causes abnormal genitalia and is cardiotoxic.[21–25] Currently, PVC medical infusion bags and tubes containing DEHP have not been banned by the European Union (EU). However, in 2005, the EU prohibited the use of phthalate plasticisers in children's toys, especially those that might be put into the mouth, such as teething rings.[26] In 2007, the supplement of European Council directive 93/42/EEC mandatorily stipulated that the phthalate content must be indicated for all medical devices.

As DEHP can leach into emulsions and reduce the surface tension of emulsion microspheres, it has been reported that DEHP will cause the collapse of emulsion microspheres, increasing the release rate of drugs in emulsion microspheres.[13,14] It was discovered in the present study that the aqueous free propofol concentration was noticeably increased after contact with an infusion extension tube. In group D, the same amount of DEHP ($1.01 \, \mu g \, ml^{-1}$) as that in group PVC was artificially added into propofol. The similar aqueous propofol concentration detected in groups PVC and D demonstrated that the main factor increasing aqueous propofol concentration is DEHP.

Because only Diprivan was studied, our results relating to the effect of PVC infusion tubes are limited to infusions of Diprivan. Other limitations of the study are the lack of a PVC-free extension tube in the control group, and the manual injection of propofol. With regard to the first

limitation, no PVC-free extension tubes are available for drug infusion, so we had to administer propofol with no extension tube. In relation to the second limitation, we did not precisely control the injection speed of propofol by means of a syringe pump. To avoid potential release of plasticiser from the rubber piston of a syringe, the use of syringes with a polypropylene piston is necessary. We found only one kind of syringe, the Becton Dickinson 20 ml syringe, which met the above requirements. When this syringe is placed on a syringe pump, an injection speed of $0.5\,ml\,s^{-1}$ cannot be achieved. This is the injection speed recommended for induction of anaesthesia with Diprivan, so we had to administer the propofol manually.

A previous study indicated that the diameter of the intravenous cannula has no impact on injection pain.[3] We used 20-gauge cannulae in the present study. Some authors have reported that the use of larger veins, such as the antecubital vein, result in less propofol injection pain.[27,28] However, most studies in the literature have involved the use of a vein in the dorsum of the hand,[1,3,5,17] and it was for this reason that we used this site of injection. However, it is a reasonable assumption that a rapid jet of propofol impinging on the endothelium of a small vein may influence injection pain. Some studies have concluded that the injection speed has no influence on pain.[3,29] Because the syringe and the infusion line are elastic, the existence of an extension tube should have no adverse influence on the impinging force on the endothelium on injection through the cannula.

In conclusion, the plasticiser DEHP can leach into propofol from PVC infusion extension tubes. These tubes are routinely used in TCI. The leached DEHP increases the aqueous propofol concentration, thereby increasing the incidence and intensity of pain due to propofol administration. To prevent the aggravation of pain caused by a propofol infusion, non-PVC infusion extension tubes should be available for use with propofol infusions.

Acknowledgements relating to this article

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