Pain on propofol injection: Causes and remedies

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Abstract:
Pain on propofol injection (POPI) is a minor problem that all anesthetists face every day. Introduction of several new formulations and hundreds of clinical trials have failed to find its remedy with just one intervention in all patients. This article highlights the causes of POPI and interventions that are used to eliminate this pain in current practice. Relevant articles from Medline and Embase databases were searched and included in this descriptive review with the following conclusions: (1) POPI is due to irritation of venous adventitia leading to release of mediators such as kininogen from kinin cascade. (2) When two or more drugs or measures are used, the incidence of POPI decreases considerably. Hence, the approach to eliminating POPI should be multimodal. (3) Any regimen that includes a drug having local anesthetic effect combined with central sedative/analgesic and rapid injection into a large vein should definitely reduce the risk of POPI to negligible levels.

Key words: Angialgia, pain on propofol injection, pain with propofol, propofol

Propofol is the most widely used intravenous (IV) anesthetic agent for induction and maintenance of anesthesia as well as for sedation inside and outside operation theater. Propofol is almost an ideal IV anesthetic agent, but pain on its injection still remains a problem. The pain may not be a serious complication, but most patients remember it as one of the unpleasant encounters with anesthetists. In one survey, pain on propofol injection (POPI) stands seventh most important problem in the current practice of clinical anesthesia.[1]

Propofol is an alkylphenol (2,6 diisopropylphenol); oil at room temperature and insoluble in aqueous solution but is highly lipid soluble. It was initially prepared with Cremophor EL, but due to anaphylactoid reactions and severe pain on its injection, it was reformulated in an emulsion. Current formulation of 1% (weight/volume) propofol is available in 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide; also disodium edetate (0.005%) is added as a bacterial growth retardant. In this formulation, the oil droplets containing most of propofol are large enough to reflect and refract white light significantly, and hence it appears milky. Its pH is 7 and pKa in water is 11; it looks viscous apart from being milky. This formulation causes pain on injection in 28%–90% of patients.[2]

Different Formulations of Propofol

Apart from pain on injection, the current lipid formulation has other disadvantages such as bacterial contamination, anaphylaxis, hyperlipidemia, and propofol infusion syndrome when used for sedation for a prolonged period. Hence, search for a better formulation continues till today. Different formulations that are tried so far are of lipid-based emulsions (with reduced lipid content),[3] nonlipid excipients (e.g., surfactants – cosurfactants, nanoparticle carriers, and cyclodextrins),[4] and a prodrug.

Lipid-Based Emulsions
Lipid-based emulsion of propofol (e.g., Ampofol) with lower lipid content contains propofol 1%, soybean oil 5%, and egg lecithin 0.6%. This formulation in one study was associated with a more frequent incidence of pain on injection compared to normal higher lipid content propofol.[3]

Widely available propofol is in long chain triglyceride (LCT) emulsion. Commonly used LCT emulsion of propofol is Diprivan (AstraZeneca). Another preparation of propofol is available in a combination of medium chain triglyceride (MCT) and LCT emulsion. Commonly available MCT/LCT propofol emulsions are Propoven (Fresenius.)

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and Propofol-Lipuro (B Braun). MCT/LCT propofol has low free propofol content and is expected to reduce pain on injection; the free propofol content is less by 30%-45% compared to LCT propofol.[9] In one observational study of 1375 patients, incidence of pain on injection of MCT/LCT propofol was 28.7%, with 16.6% of patients reporting mild pain.[9] In another study, propofol formulation 6% in Lipofundin MCT/LCT 10% had a similar incidence of pain on injection as LCT propofol containing intralipid 10%.[5] Lipofundin MCT/LCT 10% is a 10% fat emulsion consisting of MCT and LCT, whereas intralipid 10% contains only LCT.[7] In several other studies, less pain is reported with MCT/LCT preparation compared to LCT preparation.

In pediatric group of patients, also some studies have found no reduction in POPI while some studies showed a significant reduction in POPI with MCT/LCT preparation. Dilution of propofol to 0.5% in MCT/LCT produced less pain in children between 2 and 6 years, but there was an increase in triglyceride levels in blood.[9]

In a recent meta-analysis for POPI, pretreatment with lignocaine and ketamine for MCT/LCT propofol was recommended,[9] whereas in another study, addition of lignocaine did not decrease pain on injection of MCT/LCT propofol,[10] both implying that MCT/LCT propofol does not produce less pain than LCT propofol on injection.

Nonlipid Formulations
A triglyceride-free microemulsion propofol formulation utilizes nonionic surfactant and cosurfactant to emulsify propofol in water. This preparation, developed by Daewon Pharmaceuticals, Seoul, Korea, is known as Aquafol. Jung et al. reported that the pharmacodynamics and pharmacokinetic properties of this formulation were “substantially similar” to the widely available propofol formulation, but the pain on injection of this nonlipid preparation was a lot more.[11] Another lipid-free preparation of propofol has been developed containing sulfobutylether-β-cyclodextrin and water, but it does not reduce pain on injection.[12]

Prodrug
Addition of a phosphate group to propofol molecule results in the formation of water-soluble propofol. The two phosphorylated propofol prodrugs, so synthesized were named as propofol phosphate and phosphonoxyoxymethyl propofol 4 or 2,6 diisopropylphen-oxymethyl phosphate. Sodium salt of 2,6 diisopropylphen-oxymethyl phosphate is also called fospropofol, which is water-soluble and causes less pain on injection.[13] Fospropofol is available in single-use vials, as clear solution for IV administration containing 35 mg of fospropofol disodium/mL (1050 mg of fospropofol disodium in 30 mL). Usual dose is 6.5 mg/kg and is more expensive than regular propofol while it would be difficult to administer in target-controlled infusion.

Comparison of different formulations of propofol is summarized in Table 1. As can be seen from the table, problem of POPI still persists despite several attempts at changing formulation since 1977!

Causes and Mechanism of Pain on Propofol Injection
All phenols irritate skin and mucous membrane. Thus, propofol being an alkylphenol is expected to cause pain in spite of the fact that it is almost isotonic. POPI has also been described as angialgia[14] by some meaning that the pain is due to vascular involvement. POPI is immediate as well as delayed after 10–20 s.[19] The immediate pain is due to irritation of vein endothelium whereas delayed pain is due to the release of mediators such as kininogen from kinin cascade.[20]

Earlier it was hypothesized that propofol might indirectly or directly interact with sensory nerve fibers located in the venous adventitia. A recent study claims that nonselective ligand-gated cation channels such as transient receptor potential (TRP) ankyrin 1 (TRPA1) and TRP vanilloid 1 (TRPV1) are the predominant molecular entities mediating activation of peripheral nerve endings by general anesthetics.[21] TRPA1 is an ion channel located on plasma membrane of many cells and is best known as a sensor for irritants, pain, cold, and stretch. It has been shown that 97% of TRPA1-positive sensory neurons also express TRPV1 and that 30% of TRPV1-positive neurons co-express TRPA1.[22] Fischer et al.[23] performed a study on human and mouse TRPA1 with different formulations of propofol. This study revealed TRPA1 and TRPV1 as main mediators of propofol-induced pain and release of neuropeptides. The release of neuropeptides from peripheral and central terminals of sensory neurons induces vascular leakage and dilatation and is thought to contribute to neurogenic inflammation in the periphery and to central sensitization in the spinal dorsal horn. Propofol evokes a release of calcitonin gene-related peptide, a key component of neurogenic inflammation, from isolated peripheral nerves of wild type but not TRPV1 and TRPA1-deficient mice. POPI seems to be independent of gamma-aminobutyric acid A receptors, and this study identified TRPV1 and TRPA1 as key molecules for propofol-induced excitation of sensory neurons [Figure 1].

When the injection is carried out in a large vein, pain experienced is less probably due to injection in the midstream leading to minimal contact of propofol with the endothelial wall of the vein. Furthermore, the injected propofol can mix with blood freely and can have a buffering effect. Scott et al.[24] also pointed out that the speed of injection is also very important. They noticed that slow injection causes more pain than the fast injection since slow injection may increase the concentration and duration of exposure of propofol to the vein wall and rapid injection may clear the drug quickly from vein and replace
in aqueous phase. In the propofol emulsion, the drug will be distributed differently in two phases with outer aqueous phase and inner lipid phase. In a bolus injection, the outer aqueous phase comes into contact with venous endothelium causing pain.

**Remedies for Pain on Propofol Injection**

Every year, a number of studies evaluating different remedies for POPI are published; two systematic reviews in 2000 and 2011 have also been published. A quantitative systematic review in 2000 concluded that IV lignocaine (0.5 mg/kg) should be given with a rubber tourniquet on the forearm, 30–120 s before the injection of propofol to prevent pain in approximately 60% of the patients.

While the systematic review in 2011 recommends two efficacious interventions to reduce POPI, namely, injection in the antecubital vein or pretreatment with lignocaine in conjunction with venous occlusion when hand veins are used.

A third practical intervention suggested in this review was pretreatment with either lignocaine or ketamine and use of MCT/LCT propofol. The authors also suggest the use of a small dose of opioids to halve the risk of POPI. However, none of the reviews indicated elimination of POPI in 100% of patients using only one intervention.

**Drugs**

**Lignocaine**

Use of lignocaine with propofol is almost a norm since many years and hence perhaps maximum number of clinical trials were with lignocaine either alone or in combination with other drugs. The most effective dose for lignocaine with venous occlusion was 60 mg in one study, whereas 40 mg is the most commonly used dose when premixed with 200 mg of propofol. Venous occlusion with lignocaine is an effective method in relieving propofol-induced pain, Massad et al. recommend 60 s occlusion time in their report while another study did not find difference when the duration of venous occlusion was 15, 30, or 60 s. Pretreatment with lignocaine for propofol infusion did not show any benefit in pediatric group of patients in one study.

**Ketamine**

Another effective drug that has been frequently used in several clinical trials is ketamine. Most studies used ketamine...
as pretreatment while some other mixed it with propofol or applied venous occlusion after pretreatment or used in conjunction with lignocaine. The reported effective dose varied from 0.1 mg/kg to 1 mg/kg. In two studies,[32,33] a small dose 0.1 mg/kg was very effective while two other studies quoted a higher dose of 0.3 mg/kg to be effective.[34,35] Saadawy et al. found 0.4 mg/kg of ketamine better than thiopentone (0.5 mg/kg), meperidine (0.5 mg/kg), and lignocaine (1 mg/kg) as pretreatment for POPI.[36] A high dose of 1 mg/kg completely eliminated POPI, but secretion production was increased in one study.[37] In a study comparing premixed ketamine and premixed lignocaine with propofol, for decreasing POPI, lignocaine was superior in pediatric patients.[38] It is postulated that low dose of ketamine may be effective due to its peripheral local anesthetic effect whereas with high-dose central analgesic and sedative effect may be playing a role.

**Other analgesic drugs**

Other commonly used drugs are narcotics or opioids and nonsteroid anti-inflammatory drugs (NSAIDs). Narcotics or opioids and NSAIDs probably work due to their central analgesic effects while some of them do have mild peripheral local anesthetic-like effect.

Ahmad et al. have shown that incidence of POPI dropped to 13% from 32% when patients were pretreated with 100 μg of fentanyl before injecting Propofol-Lipuro mixed with 20 mg lignocaine.[39] In one study, pretreatment with lignocaine and fentanyl were compared; and lignocaine was more effective than fentanyl in this study.[40] As far back as 1990, Helmers et al. had reported a reduction in POPI with the use of fentanyl to 16% from 40%.[41]

In a small group of 175 female patients, alfentanil 1 mg and remifentanil 0.02 mg reduced the frequency and severity of pain significantly.[42] Fletcher et al. in 1994 had also shown that alfentanil in the dose of 1 mg when injected 15 s before the injection of propofol, reduced POPI significantly.[43]

Among the opioids, remifentanil was most frequently used in clinical trials in the last 10 years. In one randomized double-blinded trial, pretreatment with remifentanil (35 mcg/kg/min for 30 s) and premixed propofol with 1% lignocaine in 10:1 ratio had similar incidence of POPI (37.8%), but the combination of both had very low incidence of POPI (8.7%).[44] In one randomized double-blinded prospective trial, remifentanil, lignocaine, metoclopromide, and ketamine were compared for reduction in POPI, and lignocaine and metoclopromide were much more effective than remifentanil and ketamine.[45] In another study by Aouad et al., combination of pretreatment with remifentanil and premixing of propofol with lignocaine abolished moderate and severe pain completely and reduced mild pain significantly.[46]

**Antiemetic drugs**

Most antiemetics such as metoclopromide have peripheral local anesthetic-like effect that may help to reduce POPI. As mentioned above in one study by Polat et al., metoclopromide had similar effect as lignocaine in reducing POPI.[47]

**Inhalational agents**

Inhalational agents such as nitrous oxide (N₂O) and sevoflurane have also been used to alleviate POPI.[48–50] Both sevoflurane and N₂O have central analgesic effects and hence are used for labor analgesia. In the study using sevoflurane, the authors propose 3-fold action of sevoflurane in eliminating pain, namely, central mild analgesic action, sedative action, and vasodilatory action on the peripheral blood vessels.[51] In this study, sevoflurane 3% was used for 1 min during preoxygenation before the injection of fentanyl and propofol. Sevoflurane in combination with lignocaine abolished the POPI completely in all patients. In a recent study by Kim et al., pretreatment with inhaled 67% N₂O reduced POPI as well as pain on rocuronium injection; moreover, N₂O with or without lignocaine was superior than lignocaine alone in alleviating POPI.[47]

**Other drugs**

Other analgesics that have been tried are oral and IV paracetamol[52] and alpha-2 adrenocceptor agonists such as clonidine[53] and dexmedetomidine[54] with variable results. Furthermore, drugs such as dexamethasone (with or without lignocaine),[55] antihistamines such as diphenhydramine,[56] magnesium sulfate,[57] ephedrine,[58] and methylene blue[59] have been used with some success.

All drugs that have been used in the last 10 years in the searched clinical trials in Medline and Embase databases are summarized in Table 2.

**Other factors and interventions**

In a quantitative systematic review of POPI, in which 56 randomized controlled trials between 1981 and 1999 where 6264 adults were analyzed, there was no evidence of any relationship between the size of the IV cannula and the speed of injection and likelihood of POPI.[51] More recent trials indicate that rapid injection of propofol indeed decreases POPI.[52–54] The systematic review of 177 randomized controlled trials totaling 25,260 adults, by Jalota et al. concluded that the use of larger antecubital vein was as effective measure as pretreatment with lignocaine and venous occlusion.[55]

In the past, some authors have reported no gender difference in the incidence of POPI,[56] whereas in a recent study, POPI occurred more frequently in female patients.[57]

The other factors that may affect POPI are the temperature and pH. In the past, it was reported that when propofol injected at 4°C, the incidence of pain dropped significantly and it was postulated that low temperature probably decreases the speed of kinin cascade. In a recent study by Terada et al., topical cooling decreased the incidence of pain from 39% to 17% and when combined with lignocaine to 8%,[58] Earlier studies had indicated that warming propofol to 37°C decreased the incidence of pain from 59% to 22% albeit with risk of infection. Moreover, it was thought that high temperature might have affected mediator release and partition coefficient thereby decreasing the concentration of propofol in aqueous phase. Warming and cooling methods are not practical solutions and can be time consuming and require extreme care. Recently, Ozturk et al. have shown that alkalinizing lignocaine with 1 ml of 8.4% sodium bicarbonate for pretreatment decreased the incidence of pain significantly compared to lignocaine alone.[59]

Reducing propofol concentration to 0.5% from 1% also decreased the incidence of pain significantly in a couple of
After reviewing all studies, it is obvious that the approach to eliminate POPI should be multimodal. When only a single drug or measure was used for reducing POPI, the incidence of pain was in double digits; but when two or more drugs or measures were used the incidence of pain fell in single digits. In the last 10 years, only in three clinical trials, the incidence of POPI was 0%; [37,46,49] in one study, three drugs (fentanyl, lignocaine, and sevoflurane) were used [49] whereas in the other study, very high dose of ketamine (1 mg/kg) was used. [37] Moreover, in the third clinical trial, combination of lignocaine 40 mg and remifentanil 2 mcg/kg was premixed with propofol before use. Hence, any regimen that includes a drug having local anesthetic effect combined with central sedative/analgesic and rapid injection into a large vein should definitely reduce the risk of POPI to negligible levels.

### Conclusion

POPI is still a problem in today’s clinical practice of anesthesia despite introduction of new formulations. The pain is due to irritation of venous adventitia leading to release of mediators such as kininogen from kinin cascade. Lignocaine and ketamine are the most commonly used drugs to alleviate POPI. The approach to eliminating POPI should be multimodal. When two or more measures are used, the incidence of POPI decreases considerably. Any regimen that includes a drug having local anesthetic effect combined with central sedative/analgesic and rapid injection into a large vein should definitely reduce the risk of POPI to negligible levels.

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### Conflicts of Interest

There are no conflicts of interest.

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