Preventive methods for reducing propofol-induced pain by intravenous administration

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Graduate thesis

Zagreb, 2018.

This graduate thesis was made at the department of anesthesiology and reanimation KBC Rebro University Hospital, mentored by Prof. Dr. Sc. Dinko Tonković and was submited for evaluation in 2017/2018

LIST OF ABBREVIATIONS

POPI: Pain On Propofol Injection
I.V.: Intra-Venous
LCT: Long-Chain Triglycerides
MCT: Middle-Chain Triglycerides
TRPA1: Transient Receptor Potential Ankyrin 1
TRPV1: Transient Receptor Potential Vanilloid 1
CGRP: Calcitonine Gene Related Peptide

Table of contents

1. Summary

Title: Preventive methods for reducing propofol-induced pain by intravenous administration

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Propofol is the most widely used intra-venous (IV) anesthetic for induction and maintenance of anesthesia. Its pharmacokinetics and pharmacodynamics properties make it an almost ideal anesthetic agent, but paradoxically it is painful on injection.
Pain on propofol injection (POPI) is mostly a minor problem but its high incidence and its potentially high intensity of pain makes it important to solve in order to improve the practice of anesthesiology.
This review article highlights the causes and solutions to POPI with a chronological approach, from the discovery of propofol to the latest remedies of the current practice.
The mechanism of pain is still under investigation even though recent researches have achieved a huge step toward its understanding. It is probable that its comprehension will result in better preventive methods.
As for now, IV lidocaine seems to be the best pharmacological option in the prevention of POPI considering its availability, price and rare adverse effects.
On the other hand, recommended non-pharmacological measure to prevent POPI is rapid injection of propofol into a large vein.
Latest recommendation on the subject promote usage of a combination of local anesthetic with a central sedative and rapid injection into large vein.

Key words: Propofol, pain, prevention

2. Sažetak

Naslov: Preventivne metode za smanjivanje boli izazvane intravenskom primjenom propofola

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Propofol je najčešće korišten intra-venski (IV) anestetik za indukciju i održavanje anestezije. Njegova farmakokinetička i farmakodinamična svojstva čine ga gotovo idealnim sredstvom za anesteziju, ali paradoksalno je bolno kod injekcije.

Bol na injekciji propofola (POPI) je uglavnom manji problem, ali njegova visoka učestalost i njezin potencijalno visok intenzitet boli čine važnim pronaći rješenje kako bismo poboljšali praksu anesteziologije.

Ovaj pregledni članak ističe uzroke i rješenja POPI-a kronološkim pristupom, od otkrića propofola do najnovijih lijekova u praksi.

Mehanizam boli još je pod istragom, iako su nedavna istraživanja postigla veliki korak prema njenom razumijevanju. Vjerojatno će njegovo razumijevanje rezultirati boljim preventivnim metodama.

Kao i za sada, lidokain IV čini se najboljom farmakološkom opcijom u sprječavanju POPI-a s obzirom na njegovu dostupnost, cijenu i rijetke nuspojave.

S druge strane, preporučena nefarmakološka mjera za sprječavanje POPI je brzo injektiranje propofola u veliku venu.

Najnovija preporuka na temu promovira korištenje kombinacije lokalnog anestetika sa središnjim sedativom i brzo ubrizgavanje u veliku venu.

Ključne riječi : Propofol, bol, prevencija

3. Introduction

According to the oxford medical dictionary, anesthesia is the (1) “loss of feeling or sensation in a part or all of the body.”
The main goal of anesthesia is the temporary and reversible suppression of pain sensation and consciousness that is essential to both patient and surgeons in order to carry out surgical procedure.
This “state” is achieved in medical practice with the use of drugs, and notably propofol.

Propofol is nowadays the most widely used IV anesthetic for induction and maintenance of anesthesia.
Indeed, its anxiolytic, antiemetic and hypnotic effects combined with a very rapid onset, short half time of elimination and a favorable side effect profile make propofol a very advantageous drug for anesthesia.

During my medical studies I encountered an obvious paradox: the most widely used drug for anesthesia witch by definition is used to suppress sensations can be painful itself.
Beyond that simple yet true paradox, pain on propofol injection (POPI) can be distressing to patients and bothers anesthesiologist in their practice.

Although people suffer from pain temporarily after injection of propofol, the level of pain may be severe since about half the patient who experienced POPI recall it in the recovery room (2).

The goal of this thesis is thus to review some of the preventive measure that have been studied in order to reduce POPI.

4. Propofol

Propofol is the fruit of researches carried out in the early seventies on the alkyl derivatives of phenols group that had shown hypnotic effect in animal. Shortly after, a new molecule: 2,6-di (propan-2-yl) phenol was discovered.

The first article reporting the use of propofol in human is from 1977, where propofol (IC35868) was used for induction and maintenance of anesthesia during minor gynecological surgeries and bronchoscopies (3).

The pharmacodynamics and pharmacokinetics properties of this new drug greatly favored its global-scale utilization for induction and maintenance of anesthesia.
By depressing subcortical functions, antiemetic and anxiolytic properties are added to the main sedative-hypnotic effect of propofol.
The antiemetic effect is particularly relevant in anesthesiology considering the risk of aspiration of gastric content during intubation and the common use of opioids.

Propofol also presents the advantage of being fast acting, achieving hypnosis within forty second from the start of injection (4) with therapeutic dose. Its short half time of elimination enable a quick recovery from the anesthesia, which explain its common use for ambulatory surgery.

Only three years after its first use in vivo, in 1980, propofol is compared to methohexitone to investigate further its effect as an intra-venous anesthetic agent.
During their study, (5) the authors noted and reported pain on injection of propofol. According to the data, fifteen out of forty patient who received propofol experienced pain.

Adverse effects of propofol are rare but among them, pain on injection appears to be frequent.
It is only in 1982 (6), that prevention of POPI is first investigated which definitely shows the interest of the scientific community to counter this problem.

5. Pain on propofol injection

The injection of a drug can typically be a source of pain which presents two components. First is the pain of the puncture strictly speaking and second is the pain that may result from the injection of medicine.
Propofol is a painful agent that bothers anesthesiologist in their everyday practice.

Propofol is not the only painful drug among the intra-venous anesthetic but it is the one which aroused the most interest in research, obviously due to its wide range of indication in anesthesiology and the fact that it is a recent and safe drug.

The pain induced by propofol injection can be felt as a discomfort to an intense burning sensation that can spread from the site of injection to the entire arm.

The pain is most commonly moderate but is real because often recalled by the patient after the surgery.
Overall, it is a source of anxiety that interfere with the patient's comfort at a time of high emotional stress.

The most feared complication of pain on injection are cardiovascular event in the adult population and laryngospasm and agitation in the pediatric population.

Among 33 low-morbidity clinical outcomes assessed by expert anesthesiologists considering clinical importance and frequency, POPI was ranked seventh (7).

6. Pain incidence

It is difficult to give a precise value to the incidence of pain on propofol injection because of the wide variation of results in the scientific database.

This variation of incidence can be partly explained by the difference in age of the patients (children vs adults), different pre-treatment guidelines that may prevent pain on injection of propofol and different methods to report and characterize the eventual pain on injection.

Nevertheless, most if not all of the authors noticed the pain on injection of propofol and it is widely accepted as a common unwanted side effect.

In 2011 (8), a systematic review and meta-analysis on prevention of pain on propofol injection including more than 25000 adults patients reported the overall risk of POPI alone to be 60%.

In 2016 (9), another systematic review reported the incidence of high intensity POPI to be 38,1%.

7. Mechanism of pain

The mechanism of POPI has been investigated quite early since the discovery of propofol and is still today not fully understood.

In 1985, Briggs *et al.* noticed that POPI can be immediate on injection of propofol and/or delayed 10-20 seconds after injection (10).

Pain immediately after injection of propofol may be caused either by direct stimulation of nociceptors and free nerve endings in the venous wall or indirectly by the release of mediators, such as bradykinin, which stimulate afferent nerve endings, leading to a delayed onset of pain (11–14)

The immediate pain is easily attributable to the fact that propofol is an alkylphenol and thus a natural irritant to venous endothelium.
The delayed pain is much more complex but recent researches have brought a lot more understanding to it which gives great hope for the future of pain prevention in anesthesiology.

The first step in the understanding of the delayed pain mechanism was achieved by Matta *et al.* when they discovered the key ion channels stimulated by general anesthetics including propofol. According to their researches, TRPA1 and TRPV1 are the predominant membrane receptors mediating the activation of peripheral nerves endings by general anesthetics (15).
Matta *et al.* also showed that TRPA1 specifically mediates propofol-induced pain.

TRPV1 (Transient Receptor Potential Vanilloid 1) is a non-selective cation channel that is found on nociceptive neurons of the peripheral nervous system. TRPV1 can be activated by several endogenous or exogenous stimuli like high temperature, acidic condition and pungent compounds leading to a painful and burning sensation.

TRPA1 (Transient Receptor Potential Ankyrin 1) is non-selective ligand gated cation channel present on the plasma membrane of many cell and well-known as a sensor for environmental irritant, pain, cold and stretch. TRPA1 can be activated by a large number of noxious chemical and is thus considered as the “chemosensor” of the body (16).

In addition, endogenous inflammatory mediators can also bind to these channels. Indeed, both receptors contribute to neurogenic inflammation and pain signaling; disruption of the TRPV1 gene abolishes thermal hyperalgesia (17,18) whereas deletion of TRPA1 impairs bradykinin-induced nociception (16,19).

Fischer *et al.* deepened the researches of the delayed pain and decided to perform a study on the effects of propofol on human and mouse TRPA1. The study also identified both

TRPA1 and TRPV1 as key molecules for propofol-induced pain as well as for the release of neuropeptides (20).
Their major discovery was the release of neuropeptides such as Calcitonine Gene Related Peptide (CGRP) upon stimulation of TRPA1 receptors by propofol.
Neuropeptides release then induces vascular leakage and dilation and is believed to contribute to neurogenic inflammation in the periphery and central sensitization in the spinal horn, ultimately resulting in delayed pain.

The exact and precise mechanism is still under investigation as these data could suggest that selective TRPA1 antagonists could be an effective treatment for prevention of pain upon propofol injection.

8. Factors influencing the pain

Before the study of the exact mechanism of pain upon propofol injection, other factors though to influence the pain where reported and studied.
Thos the speed of injection, the size of the vein where propofol is injected and the concentration of propofol.

Scott *et al.* have noticed back in 1988 that there was less pain when propofol is injected in a large vein compared to small ones (arm versus hand veins), this is probably due to injection in the midstream leading to minimal contact of propofol with the endothelium lining of the vessel.
In the same way, they reported that slower injection increases the pain since it prolong the exposure of propofol in the vein (21).

It was also demonstrated several times that an increased concentration of propofol in the aqueous phase is associated with an increase pain (12,21).
This was confirmed by Doenicke *et al.* who revealed that an increase in the lipid content of propofol could reduce pain due to decreased concentration of propofol in aqueous phase (13,22).

9. Preventive measures against pain on propofol injection

Pain prevention on injection of propofol is based on the different mechanism and factors resulting in pain. Several strategies have been hypothezised and tried throughout time, the first researches dating from 1982.
On the other hand, two systematic reviews on the subject have also been published in 2000 and 2011 with interesting results even though pain prevention has never been reported to be 100% efficient so far.

9.1. Non-pharmacological prevention

9.1.1. Patient information

POPI is a possible source of anxiety for patients, as it could be suggestive of a life threatening cardiac event.
Anxiety associated with the pain on injection can most likely be reduced if the patient is well informed and knows what to expect.
Unfortunately, no researches have been conducted for this essential aspect of prevention that is information of the patient.

9.1.2. Speed injection

Slow injection prolongs the contact of propofol with the endothelium which favors release of pain mediators and increases the intensity of pain perceived by the patient.
On the contrary, a fast injection will reduce the pain on injection as propofol is flushed and rapidly replaced by blood in the vein. (12,21,23)

9.1.3. Propofol concentration

Klement W. and Arndt J.O. suggested that pain on propofol injection was directly linked to propofol concentration in the free aqueous phase.
Since propofol is highly lipophilic, the free concentration in aqueous phase depends on the proportion of lipids in the emulsion.

Thus, to test their hypothesis, Klement *et al.* studied the effect of propofol when diluted in 5% glucose and 10% intralipids.

Dilution of propofol into 10% intralipids significantly caused less pain that 5% glucose, proving that pain is related to the aqueous concentration of propofol. Pain occurred earlier and lasted longer with increasing concentration of propofol.

Those results led the authors to the conclusion that adding intralipids to propofol formulation could be a great mean of reducing pain on injection (12).

With the same idea, Soltesz *et al.* showed a significant reduction in the incidence of POPI when the concentration of propofol is reduced from 1% to 0,5% (24).

9.1.4. Temperature

McCrirrick and Hunter noted that administration of 4°C propofol could significantly reduce pain on injection (incidence from 46% to 23%) while not affecting propofol's action and efficacy (25).

On the other hand, Fletcher *et al.* found out that 37°C propofol significantly reduces pain on injection (incidence from 59% to 22%). However, the process of propofol warming up is really challenging as the risk of contamination of propofol with the water used to warm it up is high (26).

In a recent study, Terada *et al.* showed that topical cooling decreased the incidence of pain from 39% to 17% but overall, warming and cooling methods are not practical solutions and can be time consuming because of the extra care that is needed (27).

9.1.5. Site of injection

Many studies have investigated the site of injection and related pain. As said earlier, the size of the vein appears to be an important factor influencing the pain.

The fact that injection in large vein is less painful than in small veins was noted already back in 1985 by Brigg L.P. and White M., at the time the authors found out a pain incidence of 39% when propofol is injected into the dorsum of the hand compared to 3% when injected into antecubital vein (28).

It also interesting to mention here the meta-analysis from 2011 dealing with preventive measures for pain on propofol injection. They concluded that the use of antecubital vein

instead of a hand vein was the most effective intervention, having the lowest relative risk of all the methods and drugs reviewed (RR=0,14) (8).

However, the use of antecubital vein is quite unpopular because IV lines are easily dislodged when patient moves their arm, and the hand vein proves more comfortable to the patient than the antecubital vein does (9).

9.1.6. Blood aspiration

McDonald and Jameson thought about a possible buffer effect of the blood to reduce pain on propofol injection. They discovered that 2 mL aspiration of blood in the syringe prior to injection was significantly more efficient than dilution of propofol into 2mL of saline suggesting that blood may buffer or reduce the free aqueous concentration of propofol (pain incidence 58% with saline compared to 13% with blood aspiration).

On the other hand, this technic was not significantly better than adjunction of 20 mg of lidocaine to propofol (pain incidence 18% with lidocaine compared to 13% with blood aspiration) (29).

9.1.7. Formulation of propofol

Since the concentration of propofol in the aqueous phase is one the most important factor of pain on injection (12) and the fact that this concentration can be decreased by increasing the fat content of the solvent, several formulation of propofol have been tried and studied (13).

The initial formulation named Diprivan was emulsified propofol in Long Chain Triglycerides (LCT). Doenicke *et al.* noticed that propofol concentration in aqueous phase in Diprivan is relatively high suggesting that it is not completely dissolved in the lipid vehicle (22).

This led to a new formulation of propofol; lipuro-propofol: emulsified propofol in LCT and Middle Chain Triglycerides (MCT) whit lower free propofol content.

Several studies have compared both formulation (30–33), and all unanimously concluded on the superiority of LCT/MCT propofol on LCT propofol on several aspect: significant decrease

in the incidence of discomfort on injection, significant reduction in both intensity and severity of pain during target controlled infusion induction with propofol and overall reduction in POPI.

9.2. Pharmacological prevention

A vast array of drugs has been tried and are used today in the prevention of POPI. Among them lidocaine and ketamine are the most used today, but newly tried drugs are emerging as possible solutions in the prevention of POPI. It is also important to mention older trials that have permitted to understand better the mechanism of POPI.

9.2.1. Non-steroidal anti-inflammatory drugs

9.2.1.1. Aspirine

This was among the first drugs studied for prevention of POPI. Bahar *et al.* have shown in 1982 that intra-venous administration of 1000 mg of aspirine 15 minutes prior to propofol injection significantly reduced incidence of POPI, from 70% to 20% (6).

9.2.1.2. Ketorolac

Ketorolac has been tried in this indication, in their study, Huang *et al.* suggested that intra-venous pretreatment with 15 and 30 mg ketorolac could reduce POPI. The study also concluded on no venous sequelae 7 days following the procedure (34).

9.2.1.3. Diclofenac

Through a randomized, double-blind, controlled trial; Mohta *et al.* noted a significant reduction in moderate to severe pain following propofol injection for the patient who received pretreatment with 25 mg diclofenac. However, diclofenac itself was associated with mild pain in some patients (35).

9.2.1.4. Flurbiprofen

The study conducted by Nishiyama T. about the effectiveness of flurbiprofen in the prevention of POPI is particularly interesting. Indeed, according to the results, POPI was

completely abolished when 50 mg of flurbiprofen was injected intra-venously immediately before propofol (36).

More researches have thus investigated flurbiprofen in this indication considering the astonishing previous results, but results of published articles were inconsistent.
As a consequence, a meta-analysis was conducted in 2014 to appraise the efficacy and safety of flurbiprofen in reducing POPI.
They concluded that Flurbiprofen given at doses over 50mg and preceded by venous occlusion was effective in preventing or relieving POPI.
Flurbiprofen seem to be a promising prophylactic agent in the control of propofol pain although more studies are required to assess its adverse effects (37).

9.2.2. Opioids

9.2.2.1. Fentanyl and Alfentanil

Several studies have been done on utilization of opioids for the prevention of POPI.
Helmers *et al.* have shown that pretreatment with 0,5 mg alfentanil before propofol injection reduces pain incidence form 40% to 16% (38).

Nathanson *et al.* have tried 1mg alfentanil pretreatment injected 15 and 30 seconds prior to propofol with significant reduction on POPI : 84% to 36% and 67% to 24% respectively (2).
Fletcher *et al.* in 1994 had also shown that 1mg alfentanil injection 15 seconds before injection of propofol reduced POPI significantly.

Like aspirin, fentanyl was studied by Bahar *et al.* back in 1982. They have noted a reduction in severity of POPI but not in the overall pain incidence after injection of 0,1 mg 3 to 5 minutes prior to propofol injection (6).

9.2.2.2. Remifentanil

Remifentanil has been subjected to many clinical trials for prevention of POPI.
In one study, pretreatment with remifentanil and premixed propofol with 1% lidocaine was compared with either treatment alone in the prevention of POPI.

Pretreatment with remifentanil and premixed propofol and lidocaine had equivalent incidence of POPI (37,8%). However the combination therapy achieved very low incidence of POPI (only 8,7%) (39).

Aouad *et al.*, also have studied pretreatment with remifentanil and lidocaine-propofol premixture and the combination of both. The result obtained in this study were very similar to the previous one with a decrease in the incidence of POPI in the remifentanil group (36% pain incidence) and lidocaine premixture (35% pain incidence) as well as very good results in the combination group (9,6% pain incidence). The authors also noted that moderate and severe pain were completely abolished when both drugs were combined while mild pain was reduced significantly (40).

9.2.2.3. Tramadol

Some studies have assessed the probable local anesthetic effect of tramadol for the prevention of POPI.
In two studies, Tramadol was given intra-venously at the dose of 50mg after occlusion of the vein with a tourniquet and was kept for 1 minute before re-opening of the venous sytem and injection of propofol.
Both studies concluded in a significant reduction of pain incidence on propofol injection (41,42).

9.2.3. Ketamine

Ketamine is a frequently studied drug given its efficacy in our indication of interest.

In 1999, Tan *et al.* have shown that pretreatment with 10mg ketamine injected 30 seconds before propofol could reduce significantly pain incidence of propofol from 84% to 26%.
They have postulated a peripheral local anesthetic mechanism rather than a central anesthetic because of the low dose used in their study (0,2 mg/kg) (43).

Other dosage and techniques for prevention of POPI with use of ketamine are reported.
Small dosage of ketamine (0,1mg/kg) have been reported effective in several studies (44,45); higher dosage (0,3mg/kg) was found to be effective too (46,47).

Another study highlighted the efficacy of ketamine at higher doses; they concluded that pretreatment with 1mg/kg completely eliminated pain associated with injection of propofol while pretreatment with 0,5 mg/kg only reduced the incidence and intensity of pain (48).

One of the goal of the study was also to take into account the side effects associated with higher dose of ketamine: with a dose of 1mg/kg, hemodynamics was not affected but they reported increased secretion.

Although ketamine's results are satisfactory for the prevention of POPI, a study comparing the efficacy of pretreatment with various drug have concluded that lidocaine and metoclopramide pretreatment were superior to ketamine (0,1mg/kg dosage) and remifentanil (49).

9.2.4. Metoclopramide

Metoclopramide is an antiemetic drug with a peripheral local anesthetic-like effect given the fact that its structure is analog to procaine.

One of the first study on prevention of POPI with use of metoclopramide dates from 1992. The authors, Ganta and Fee, have shown that administration of 5mg metoclopramide immediately before propofol injection in the dorsum of the hand could significantly reduce pain incidence on propofol injection (50).

Later in 1999, Liaw *et al.* decided to compare three different technique of administration of metoclopramide: administered intra-venously immediately before injection of propofol, after mixing with propofol, or after a rubber tourniquet for 1 minute before propofol injection. Metoclopramide was compared to lidocaine and saline to evaluate the most effective method.

They concluded that Intra-venous retention of 10 mg metoclopramide for 1 minute was great in regard of prevention of POPI, achieving incidence of pain as low as 36%. There was no significant difference between metoclopramide and lidocaine which permitted to legitimate metoclopramide as an useful alternative in the prevention of POPI (51).

Finally and as mentioned before, Polat *et al.*, have noted that pretreatment with 10mg metoclopramide was among the best pharmacological prevention method with pain reduction as high as 76% (49).

9.2.5. Inhalation agents

Nitrous oxide and sevoflurane have also been used to prevent POPI since both have central analgesic effects.

In one study, the authors proposed a triple actions of sevoflurane toward POPI elimination: central mild analgesic action combined with a sedative action and a vasodilation on the peripheral blood vessels (52). The study concluded in no significant difference in the reduction of POPI between sevoflurane alone and lidocaine alone but when combined together with a premedication of fentanyl POPI was completely abolished in all patients.

Regarding nitrous oxide, Kim *et al.* found out that pretreatment with inhaled 67% nitrous oxide reduced POPI; moreover, nitrous oxide with or without lidocaine was better than lidocaine alone (53).

9.2.6. Lidocaine

Lidocaine is the most widely used drug in the practice for the prevention of POPI being both effective and available, and thus has been the most widely studied drug in this indication too.

Various concentration and dosages of lidocaine, or combination with other measures for reducing POPI has been extensively evaluated and seems to be one of the most promising drug in this condition.

To reduce POPI, lidocaine is administered either by mixing with the propofol and injecting both together, or by injecting separately, as an intravenous pretreatment prior to the propofol injection.

9.2.6.1. Pretreatment

The use of lidocaine as pretreatment is based on its supposed local anesthetic effect on the vein. Venous occlusion up to 120 seconds permits to increase the contact of lidocaine with venous intima responsible for the inhibition of the enzymatic cascade responsible for the liberation of mediators such as kinin.

Several studies have investigated this technique with different dosage of lidocaine and different timing of injection.

McCulloch and Lees have shown back in 1985 that administration of 10 mg lidocaine immediately before injection of propofol into the dorsum of the hand could reduce pain incidence from 37,5% to 17,5% (54).

Genta and Fee reported a pain incidence reduction from 49,4% to 21,1% with the same dosage and timing (50). Lyons *et al.* have noted that 10mg lidocaine pretreatment injected 10 seconds before propofol could reduce pain incidence from 64% to 44% (55).

Nicol *et al.* have concluded on a pain incidence reduction from 51% to 35% with 10mg lidocaine pretreatment injected 15 seconds before propofol (56).
Interestingly, Massad *et al.* recommended a 60 seconds venous-occlusion time before 20 mg propofol injection in one report in 2006 (57), while 2 years later in 2008 they found no difference with different timing of venous occlusion (15, 30 or 60 seconds) (58).

Another recent randomized, double-blind, controlled study have investigated pretreatment technique with 20 mg lidocaine and different vein occlusion timing (0, 15, 30, 60 seconds. They concluded that pretreatment with 20 mg with or without venous occlusion significantly reduces incidence and intensity of POPI; in addition, 60 seconds occlusion of the vein with 20 mg lidocaine was found to be the most effective (59).

Despite the wide array of results in term of dosage and venous occlusion timing, it is clear that pretreatment technique is among the best prevention technique for POPI.
This is notably well illustrated by a quantitative systemic review conducted in 2000 by Picard and Tramèr which concluded that IV lidocaine pretreatment (0,5 mg/kg) 30-120 seconds before propofol injection could prevent POPI in approximately 60% of patients (60), being the best prevention measure reviewed at the time.

In 2011, another systematic review placed lidocaine pretreatment with hand vein occlusion as one of the best two techniques available for the prevention and reduction of POPI (8).

9.2.6.2. Admixture

The mechanism of this technique which consist of mixing lidocaine and propofol together and then inject the mixture is not fully understood today.

One hypothesis is that lidocaine mixed with propofol could reduce the free aqueous concentration of propofol and thus reduce pain (61). Just as pretreatment technique, admixture technique was subjected to various results but again all showing a reduction in POPI.

Back in 1990, Newcombe *et al.* already reported the significant drop in severity and frequency of POPI (from 86,9% to 48,9%) when 10mg lidocaine is mixed to propofol (62).
Many researches have also concluded in reduction of POPI with admixture techniques, with dosage from 10 to 40mg of lidocaine (61,63,64).

A possible problem of the mixture is linked to its physicochemical unstability. According to Masaki *et al.* the addition of lidocaine to propofol results in an increase in oil droplet diameter emulsion. This reaction is time- and dose-dependent and may cause pulmonary embolism depending on the dose of lidocaine (65).

9.2.6.3. Comparison between pretreatment and admixture

Picard and Tramèr suggested that pretreatment with venous occlusion was more effective than admixture to reduce POPI (60). Indeed, venous occlusion with a tourniquet allowed high concentration of lidocaine to be retained locally thus extending the analgesic time (9).

Also, the pretreatment technique involves much more steps and take much more time than admixture which makes it inappropriate in some circumstances such as rapid induction, encouraging anesthesiologist to prefer admixture over pretreatment technique.

Nevertheless, the efficacy of both techniques has been proved and a 2016 systematic review including 84 randomized controlled trials for a total of 10 460 adult patients concluded in no significant difference between the two techniques.
The analyzed data permitted to confirm that both techniques were equivalently effective in reducing POPI. Overall pain incidence is reduced from 64% to 30,2% and high intensity pain is reduced from 38,1% to 11,8%.

The authors thus recommend lidocaine administration by any method, admixture or pretreatment depending on the anesthesiologists' circumstances and appropriateness.
On top of that, thrombophlebitis, a potential adverse effect of lidocaine was rare and only reported in 2 studies (9).

The results of this systematic review is probably placing lidocaine as the best single drug for the prevention of POPI, being available worldwide, cheap and with rare adverse effects.

9.2.7. Other drugs

Many other drugs have been tried with variable success, notably oral and IV paracetamol (66), clonidine-ephedrine combination (66), dexamethasone with or without lidocaine (67) but also magnesium sulfate (68) and methylene blue (69).

10. Conclusion

Despite many trials and researches POPI is still a problem today.
The mechanism of pain is still under investigation and will probably greatly help in solving the problem when eluded.
Until our understanding of the mechanism improve and/or new drug are developed; lidocaine seems to be the best option at the moment, being cheap, available, safe and offering great results.
According to a recent review, our approach in the prevention of POPI should be multimodal, with recommended use of drug regimen with local anesthetic effect combined with central sedative/analgesic and rapid injection into a large vein (70).

11. Acknowledgement

I would first like to acknowledge the University of Zagreb, school of Medicine who gave me the opportunity to pursue medical studies in the beautiful country of Croatia. I am forever grateful.

Likewise, I would like to thank my mentor Professor Dinko Tonkovic from the department of Anesthesiology and resuscitation medicine for his patience and availability.

I would also like to thank Dr. Arthur Neuschwander for his infallible help during my internship of anesthesiology.

My final gratitude goes to my life partner and my family, they are the backbone to my success, thank you for your support in all aspects of life.

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13. Biography

I was born in Nice, France in 1990. After high school, with a great interest in sciences and the will to help others I decided to study medicine.

After failing the entrance exam of the University of Montpellier, I decided to look abroad in the pursue of my dream. I easily decided to move to Croatia and study medicine in Zagreb.

I now resides in Paris, France and I am preparing internship to become a surgeon.