Prevention of Pain on Injection with Propofol: A Quantitative Systematic Review

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The best intervention to prevent pain on injection with propofol is unknown. We conducted a systematic literature search (Medline, Embase, Cochrane Library, bibliographies, hand searching, any language, up to September 1999) for full reports of randomized comparisons of analgesic interventions with placebo to prevent that pain. We analyzed data from 6264 patients (mostly adults) of 56 reports. On average, 70% of the patients reported pain on injection. Fifteen drugs, 12 physical measurements, and combinations were tested. With IV lidocaine 40 mg, given with a tourniquet 30 to 120 s before the injection of propofol, the number of patients needed to be treated (NNT) to prevent pain in one who would have had pain had they received placebo was 1.6. The closest to this came meperidine 40 mg with tourniquet (NNT 1.9) and metoclopramide 10 mg with tourniquet (NNT 2.2). With lidocaine mixed with propofol, the best NNT was 2.4; with IV alfentanil or fentanyl, it was 3 to 4. IV lidocaine before the injection of propofol was less analgesic. Temperature had no significant effect. There was a lack of data for all other interventions to allow meaningful conclusions. The diameter of venous catheters and speed of injection had no impact on pain. **Implications:** IV lidocaine (0.5 mg/kg) should be given with a rubber tourniquet on the forearm, 30 to 120 s before the injection of propofol; lidocaine will prevent pain in approximately 60% of the patients treated in this manner.

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A disadvantage of propofol is pain on injection, which is sometimes very distressing to patients. Among 33 clinical problems, propofol-induced pain has been ranked seventh, when both clinical importance and frequency were considered (1). Many different methods have been proposed to reduce the incidence and severity of this adverse effect of propofol. The aim of this quantitative systematic review was to test, with the best available evidence, the relative efficacy of analgesic interventions that have been used to prevent pain caused by propofol injection.

Methods

We conducted a systematic search for reports of randomized, controlled trials that tested the analgesic effect of prophylactic interventions (active) compared with placebo or "no treatment" (control) on pain on injection with propofol. When physical measurements were tested, the group with propofol (as manufactured) was regarded as a "no treatment" control. For instance, when cold (i.e., 4°C) propofol was tested, propofol at room temperature (i.e., 23°C) was regarded as control. We searched the MEDLINE (Datastar and PubMed, from 1966 to September 1999), COCHRANE Library (1999, issue 3), and EMBASE (from 1982 to February 1999) databases without restriction to the English language and by using different search strategies with the free text key words "propofol," "pain," "injection," and "random," and a combination of these words. Additional trials were identified from reference lists of retrieved reports and review articles on propofol and pain on injection (2,3), and by manually searching locally available anesthesia journals. We did not contact the manufacturers of propofol. Authors were contacted if there was ambiguity about data. We did not consider data from abstracts. Reports on experimental pain and comparisons without a placebo- or a "no treatment-" arm were not analyzed.

Both authors independently read each report that could possibly meet the inclusion criteria and scored them for inclusion and methodological validity using the three-item, five-point, Oxford scale (4). We then reached a consensus by discussion. The scale takes

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into account proper randomization, double-blinding, and reporting of withdrawals and drop-outs. The minimum score of an included randomized controlled trial is one, the maximum score is five.

We noted information about patients (adults or children), size and site of venous cannulation, speed of injection of propofol, and analgesic interventions from each included report. Different scores of pain measurement (for instance, visual analog or verbal rating scales) were used in these trials. Combining these data was impossible. We therefore decided to extract dichotomous data on complete absence of pain. This dichotomous hurdle may be unnecessarily high. An experimental intervention that does not completely prevent pain may alleviate most symptoms. Such an intervention may, of course, be very useful. However, to extract homogeneous data and to minimize the risk of bias caused by different definitions of endpoints, we decided to concentrate on a clearly defined hard endpoint. Complete absence of pain is such an endpoint.

We calculated relative "benefit" as relative risk with 95% confidence interval (CI) (5), using a fixed-effect model to combine data (6). As an estimate of the clinical relevance of the analgesic efficacy, we calculated the number needed to treat (NNT) (7) using the weighted means (weighted by the sample size) of the event rates of active and control interventions. A positive NNT indicated how many patients had to be exposed to an active intervention to prevent pain in one who would have had pain had they all received control (i.e., propofol without the analgesic intervention). A 95% CI around the NNT point estimate was obtained by taking the reciprocals of the values defining the 95% CI for the absolute risk reduction (8). A statistically significant treatment effect was assumed when the 95% CI around the relative benefit excluded 1; the 95% CI around the NNT would then contain positive numbers only.

Results

Seventy potentially relevant reports were retrieved, published between 1981 and 1999. Fifteen reports were subsequently excluded. Four were not randomized trials (9–12). In six, a placebo or "no treatment" group was lacking (13–18). Three reports were excluded for different reasons: pain outcomes were not dichotomous (19), the study was on experimental pain only (20), or the number of patients per group was not reported (21). There was strong suspicion that the same data have been used in three different full reports (22–24); because the original authors were unable to clarify this, we analyzed the data from only one report (23).

We analyzed data from 56 randomized, controlled trials (6264 patients) (17,23,25–78). Average trial size was 111 patients (range, 28 to 368). The median quality score was 2 (range, 1 to 4). Three reports were published as letters (44,63,73); in one a pseudo-randomization method (allocation according to medical record number) was used (27), and in one randomization was unclear (63). These five reports were included in the analysis. Six trials (11%) reported an appropriate method of blinding (identical ampoules, for instance). In 18 trials (33%), there was no attempt for any blinding. Authors of four trials acknowledged support from the manufacturer (35,44,48,56). Three studies were performed in children (31,34,74), two in both adults and children (32,70); all others were in adults only. In all trials, propofol was injected into the upper limb.

Subgroup Analyses

We performed three subgroup analyses to test the propriety of pooling data. This was done with data from control patients only. In seven trials, propofol was injected into an IV catheter "on the forearm" (41,46), in the cephalic vein (45,72,73), or in both a vein on the back of the hand or the forearm (44,49): 261 of 385 controls (68%; range 24% to 80%) reported pain on injection with propofol. In 49 trials, IV catheters were placed exclusively on the back of a hand: 1156 of 1674 controls (69%, range 10% to 100%) reported pain on injection. The difference between these two subgroups was not statistically significant, relative risk 1.02 (95% CI 0.94 to 1.10, $P > 0.05$). In 43 trials, propofol was injected on the dorsum of a hand, and the diameter of the catheter (median 21-gauge; range 17- to 23-gauge) was reported. In 45 trials, IV catheters were placed on the back of a hand, and the speed of injection of propofol (average 0.6 mL/s; range 0.125 to 2.0 mL/s) was reported. Graphically, there was no evidence of any relationship between the size of the catheter or the speed of injection and the likelihood of pain on injection with propofol (Figure 1). Thus, we pooled efficacy data according to experimental interventions and doses, whenever appropriate.

Analgesic Interventions

IV lidocaine, fentanyl, alfentanil, meperidine, metoclopramide, and temperature were each tested in more than two trials. All results were, except for temperature, statistically significant in favor of the analgesic interventions (Table 1, Figure 2).

Lidocaine. Lidocaine was given before the injection of propofol (Table 1A) or mixed with propofol (i.e., made up to a total volume of 20 mL) (Table 1B) or given IV with a tourniquet (i.e., as a Bier's block in the isolated arm) (Table 1C). Bier's blocks were usually described as rubber tourniquets on the forearm; when pressure of the tourniquet was reported, it was between 50 and 70 mm Hg, and it was applied for 30 to 120 s. With this technique, the NNT to prevent any

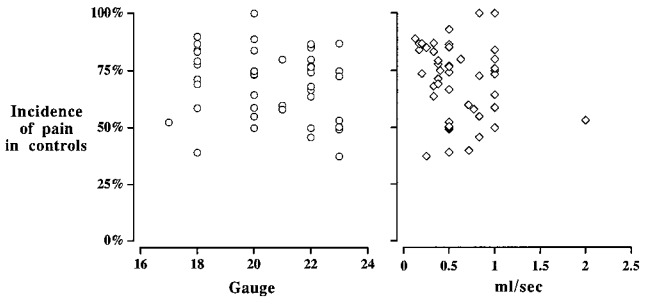

Figure 1. Relationship between diameter of IV catheters (Gauge) and speed of injection of propofol, respectively, and the incidence of pain on injection of propofol (i.e., in patients who did not receive any analgesic intervention). Subgroup analyses in patients who had a catheter placed on the dorsum of the hand. Each symbol represents one trial. Symbol sizes do not take into account trial sizes.

pain compared with placebo was 1.6 to 1.9 (Table 1C). IV lidocaine given before propofol (i.e., without a tourniquet) and lidocaine mixed with propofol were less effective (Table 1, A and B). In one trial, lidocaine 100 mg was given IV to 22 patients 1 min before the injection of propofol; this was not different from placebo (42).

Opioids. In two trials, some patients received fentanyl or alfentanil immediately before the injection of propofol (32,34). We considered this method *a priori* as insufficiently analgesic in this context; these data were, therefore, not analyzed further. With alfentanil, fentanyl, or meperidine, given minutes before the injection of propofol, NNTs were between 3 and 4 (Table 1D). When meperidine 40 mg was given with a tourniquet, the NNT was 1.9. Alfentanil 10 μg/kg, tested in 51 adults (75), had an NNT of 4.3 (95% CI 2.5 to 15); alfentanil 20 μg/kg, tested in 20 children (34), had an NNT of 1.4 (95% CI 1.1 to 2). With fentanyl 100 μg or 150 μg (adults only) (23,28,44,49), the NNT was 4.

Metoclopramide. The NNT of IV metoclopramide 5 or 10 mg, given before the injection of propofol, was 2.7 (Table 1E). When injected with a tourniquet, the NNT decreased to 2.2.

Temperature

Cooled (i.e., 4°C) propofol and warmed (i.e., 37°C) propofol had no statistically significant analgesic effect (Table 1E).

Other Interventions

IV thiopentone, lidocaine 60% tape, and nitroglycerine ointment were each tested in two trials. For thiopentone (42,50) and nitroglycerin (61,76), the respective trials produced contradictory results. With lidocaine tape (72,78), pain of both insertion of IV lines and of injection of propofol was decreased. All other pharmacological or physical interventions were each tested in one trial: IV ondansetron, droperidol, nafamostat mesilate, ketamine, aspirin, ketorolac, prilocaine, or morphine; premedication with oral diazepam or IM ketorolac; iontophoresis with lidocaine; dilution of propofol with homologous blood or dextrose; speed of injection of propofol or of carrier; long chain triglycerides; tourniquet; double or single lumen IV sets; and site of injection. No meaningful conclusions could be drawn. In one trial, pretreatment with IV fentanyl was used concomitantly with a propofol-lidocaine mixture (49); this was more analgesic than either treatment alone. In another trial, none of 40 patients receiving pretreatment with fentanyl plus cold propofol mixed with lidocaine reported any pain (17). Reports on adverse effects were sparse. No data on costs were retrieved.

Discussion

In these systematically searched randomized, controlled trials, approximately 70% of all control patients reported some degree of pain or discomfort on injection with propofol alone. In some trials, all controls reported pain. The most effective analgesic method was IV lidocaine, given as a Bier's block before the injection of propofol. Of 100 the patients treated with lidocaine 40 mg with a rubber tourniquet at the forearm for 30 to 120 s before the injection of propofol, approximately 60 (NNT 1.6) will not have any pain who would have had pain had they not received lidocaine. A dose-response, with a dose range of 20 to 100 mg, was not obvious. This applies to the injection of propofol into the upper limb in adult patients. No trial tested the effect of an analgesic intervention when propofol was to be injected into the lower limb. Also, only limited data were from children. We have to assume that the most effective analgesic method in adults may be extrapolated to children. Thus, the pediatric lidocaine dose for an effective tourniquet method is approximately 0.5 mg per kg of body weight.

We generated comparisons between treatment options (Figure 2). Conclusions derived from such a "league table" of relative efficacy must be interpreted cautiously, because confounding variables cannot be excluded. The data suggested that, for best efficacy, it may not be worthwhile, compared with the lidocaine-tourniquet method, to give lidocaine IV before the injection of propofol or to mix it with propofol. Of 100 the patients treated with lidocaine 20 mg, 53 patients (NNT 1.9) will not have any pain when a tourniquet is used, 42 (NNT 2.4) will be pain-free when the lidocaine is mixed with propofol, and only 25 (NNT 4.0) will profit, when the lidocaine is given before propofol (Table 1, A–C).

Table 1. Prevention of Pain on Injection with Propofol: Efficacy Data

Active	Incidence of pain on injection (%)		Total Patients (*n*)		Patients without Pain (*n*)		RB	Lower 95% CL	Upper 95% CL	NNT	Lower 95% CL	Upper 95% CI	Trials (*n*)	References
	Active	Control	Active	Control	Active	Control								
A. Lidocaine (mg) given before the injection of propofol														
10	54.8	69.4	301	297	136	91	1.50	1.29	1.74	6.9	4.5	15	6	30, 40, 53, 56, 60, 67
20	29.4	54.3	68	70	48	32	1.54	1.15	2.07	4.0	2.5	11	2	50, 68
40	76.7	100	30	30	7	0	n/a			4.3	2.6	12	1	42
B. Lidocaine (mg) mixed with propofol 200 mg														
5–8	68.3	84.2	243	241	77	38	1.67	1.39	2.00	6.3	4.3	12	4	29, 41, 48, 65
10–12	55.5	80.8	389	401	173	77	2.00	1.71	2.33	4.0	3.2	5.3	10	32, 39, 41, 43, 48, 59, 65, 67, 71, 74
20–24	38.3	80.1	329	332	203	66	3.10	2.46	3.91	2.4	2.1	2.9	9	32, 35, 39, 41, 47, 48, 57, 61, 71
30–40	52.1	79.6	219	201	105	41	3.13	2.36	4.15	3.6	2.8	5.3	6	32, 39, 49, 58, 71, 78
C. Lidocaine (mg) with tourniquet														
20	23.9	76.6	46	47	35	11	3.26	1.89	5.60	1.9	1.4	2.8	2	25, 47
40	15.5	71.7	97	99	82	28	2.99	2.16	4.15	1.8	1.5	2.2	4	47, 51, 52, 77
60	11.4	74.3	35	35	31	9	3.44	1.94	6.12	1.6	1.2	2.2	1	23
100	36.8	90.0	19	20	12	2	6.32	1.62	24.6	1.9	1.3	3.6	1	54
D. Opioids														
Fentanyl 100 or 150 μg, or 2 μg/kg	38.5	66.4	148	149	91	50	1.84	1.44	2.35	3.6	2.6	5.9	5	23, 28, 31, 44, 49
Alfentanil 1000 μg, 10 or 20 μg/kg	24.7	56.2	194	185	146	81	1.74	1.46	2.09	3.2	2.5	4.5	6	34, 36, 44, 58, 75, 77
Meperidine 25 mg, before	34.6	63.8	52	47	34	17	1.81	1.18	2.77	3.4	2.1	9.7	1	53
Meperidine 40 mg, tourniquet	22.7	75.4	66	65	51	16	3.14	2.01	4.90	1.9	1.5	2.6	2	23, 64
E. Metoclopramide														
5 or 10 mg, before	22.2	59.3	135	135	105	55	1.91	1.53	2.39	2.7	2.1	4	3	30, 40, 51
10 mg, tourniquet	30.7	76.0	75	75	52	18	2.89	1.88	4.44	2.2	1.7	3	2	51, 62
F. Temperature														
Cold (4°C)	65.7	70.5	169	173	58	51	1.16	0.85	1.59	21	6.8	−20[a]	6	29, 52, 55, 63, 65, 73
Warm (37°C)	54.7	67.0	95	106	43	35	1.44	1.00	1.99	8.2	3.9	−84[a]	3	37, 63, 73

RB = relative benefit, NNT = number needed to treat, CL = confidence limit, before = injected into the same IV catheter before the injection of propofol, mix = added to propofol to a volume of 20 mL, tourniquet = usually a rubber tourniquet on the forearm, 30–120 s before the injection of propofol.

[a] The negative upper limit of the 95% CI of the NNT indicates lack of a statistically significant analgesic effect.

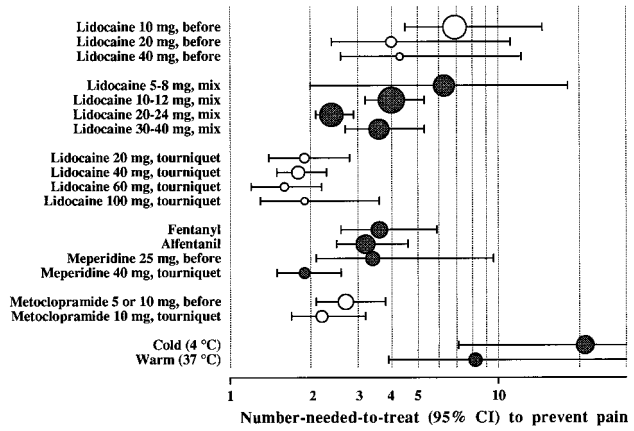

Figure 2. League table of the relative analgesic efficacy of interventions which are used to prevent pain on injection with propofol. Symbol sizes are proportional to the number of analyzed data. Only the most frequently used interventions are shown. before = lidocaine given IV before propofol, mix = lidocaine mixed with propofol 200 mg, tourniquet = for instance, a rubber tourniquet (for 30 to 120 s) on the forearm, CI = confidence interval. For "cold" propofol and "warm" propofol, the comparator was propofol at room temperature.

IV opioids showed less efficacy compared with the lidocaine-tourniquet technique. Meperidine looked promising, when given as a Bier's block (23,64). This may be regarded as further evidence of meperidine's local-anesthetic properties (79). In one trial, the concomitant use of naloxone did not reduce meperidine's efficacy, suggesting that its peripheral analgesic effect is not mediated by opioid receptors (23). Fentanyl and alfentanil were also given as Bier's blocks (64,77), although with less success compared with meperidine. Systematic review was unable to confirm any relevant peripheral analgesic efficacy with Bier's block with opioids other than meperidine (80).

Bier's block with metoclopramide decreased propofol-induced pain (Table 1E). Metoclopramide has been shown to possess weak local anesthetic properties (81); its chemical structure is an analog of procaine.

Early trials reported significant analgesic efficacy when propofol was cooled to 4°C immediately before injection (29,55) or, oppositely, when it was warmed to 37°C (37). These results could not be confirmed in subsequent studies (52,63,65,73). The combined analysis suggested that temperature has no relevant effect on propofol-injection pain. There was a lack of data for all the other analgesic interventions to allow meaningful conclusions.

There were two further interesting findings. First, there was no evidence of any relationship between catheter size and the incidence of pain on injection (Figure 1). Thus, as expected, catheter size *per se* is of no importance. No relationship could be established between injection pain and size of veins, because original reports did not provide relevant data. There was evidence from two randomized trials that the incidence and severity of pain with propofol can be reduced when the drug is injected into a vein in the antecubital fossa (56,67). It is, however, unlikely that anesthetists will choose the antecubital fossa vein routinely to avoid propofol-injection pain. The second additional finding was unexpected. There is a widely held view that slow injection of propofol may increase the likelihood of pain. This assumption refers to an early publication in which 15 patients had been randomized to slow injection of propofol (67). In these trials, a wide range of injection speeds were tested (i.e., 0.125 to 2 mL/s); there was no evidence of any impact of speed of injection on the incidence of pain (Figure 1).

Several combination therapies were tested. However, it may be overoptimistic to try to further improve the degree of analgesic efficacy as seen with the lidocaine-tourniquet method; incidences of pain were very low (Table 1C). The best NNT which can be achieved for efficacy is 1. All control patients would have to report pain on injection with propofol, and none who receives the active intervention; this is unlikely with any analgesic intervention. Also, combination therapies may increase cost and the risk of adverse drug reactions, and they may be circumstantial in daily clinical practice.

Some doubt remains concerning the scientific validity of some of these trials. Surely, almost 20 years after the advent of propofol, it is difficult to accept that the injection of this innovative and widely used IV anesthetic still causes pain, and that the mechanisms of that pain are still obscure. The lack of sponsorship from the manufacturer for most of these trials may be a result of a lack of interest. Perhaps as a consequence, a research program was not obvious, although some trials were designed to study peripheral pain mechanisms. More than 6200 patients have been randomized in 56 trials during the past 18 years. According to the instrument of critical appraisal we used (4), most trials were of rather poor quality. Blinding, for instance, was often inadequate, leaving the trials open to the risk of observer bias. Numerous pharmacological treatments, different doses and combinations, alternative methods of administration, and physical interventions were tested, often without a clear biological basis. Propofol has been warmed or cooled, injected faster or more slowly, with or without a tourniquet, diluted or not. Local anesthetics, opioids, nonsteroidal antiinflammatory drugs, ketamine, metoclopramide, droperidol, and other chemical substances have been tested. The lidocaine-tourniquet method is undeniably effective and simple to perform. This begs the question as to the necessity of clinical studies that may identify yet another intervention with some analgesic efficacy to prevent pain on injection with propofol.

In conclusion, for best prevention of pain on injection with propofol, lidocaine 0.5 mg/kg should be given with a rubber tourniquet before the propofol injection; of 100 treated patients, approximately 60 have no pain.

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