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Reduction of pain during induction with target-controlled propofol and remifentanil

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Background. Pain on injection of propofol is unpleasant. We hypothesized that propofol infusion pain might be prevented by infusing remifentanil before starting the propofol infusion in a clinical setting where target-controlled infusions (TCI) of both drugs were used. A prospective, randomized, double-blind, placebo-controlled trial was performed to determine the effect-site concentration (Ce) of remifentanil to prevent the pain without producing complications.

Methods. A total of 128 patients undergoing general surgery were randomly allocated to receive normal saline (control) or remifentanil to a target Ce of 2 ng ml^{-1} (R2), 4 ng ml^{-1} (R4), or 6 ng ml^{-1} (R6) administered via TCI. After the target Ce was achieved, the infusion of propofol was started. Remifentanil-related complications were assessed during the remifentanil infusion, and pain caused by propofol was evaluated using a four-point scale during the propofol infusion.

Results. The incidence of pain was significantly lower in Groups R4 and R6 than in the control and R2 groups (12/32 and 6/31 *vs* 26/31 and 25/32, respectively, $P<0.001$). Pain was less severe in Groups R4 and R6 than in the control and R2 groups ($P<0.001$). However, both incidence and severity of pain were not different between Groups R4 and R6. No significant complications were observed during the study.

Conclusions. During induction of anaesthesia with TCI of propofol and remifentanil, a significant reduction in propofol infusion pain was achieved without significant complications by prior administration of remifentanil at a target Ce of 4 ng ml^{-1}.

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The use of target-controlled infusion (TCI) has become a useful technique for total i.v. anaesthesia owing to the development of sophisticated infusion pumps, short-acting anaesthetics, and pharmacokinetic models. Propofol and remifentanil are a valuable combination for TCI because of their similar properties, including rapid onset and short action time. However, pain on infusion of propofol during induction of anaesthesia remains a problem. In one study, 68% of patients who received propofol reported considerable pain on injection.[1] Expert anaesthesiologists ranked propofol injection pain during induction as seventh among 33 clinical anaesthesia outcomes in frequency and importance.[2] Many techniques have been suggested to prevent the pain, with varying success. They include premedication,[3] use of local anaesthetics,[4 5] dilution of propofol,[6] and pre-treatment with systemic opioids.[7 8] However, these methods have failed to gain popularity among anaesthesia providers because cumbersome preparations are required and they do not completely prevent the injection pain.

Several investigators have reported that remifentanil administered via bolus injection or continuous infusion is effective in reducing propofol injection pain.[9–11] We hypothesized that injection pain during TCI with propofol and remifentanil could be prevented by allowing the effect-site concentration (Ce) of remifentanil to reach a level effective for pain prevention before infusing propofol. The need for additional drugs or equipment would be

eliminated because remifentanil is an integral part of the anaesthetic technique. However, the absence of opioid-related complications during the administration of remifentanil must be demonstrated.

In the current study, we aimed to identify the target Ce of remifentanil needed to prevent pain from the propofol infusion during TCI using a combination of propofol and remifentanil.

Methods

This study received institutional review board approval, and written informed consent was obtained from subjects. One hundred and twenty-eight ASA I–II adult patients aged 16–70 yr and undergoing elective general surgery, such as thyroid surgery, breast surgery, and laparoscopic cholecystectomy, were included in the study. Exclusion criteria were: patients with known allergy to egg lecithin or soybean oil, severe neurological deficits or psychiatric disorders, and patients receiving current pain medication or having previous history of drug abuse.

The patients were randomly assigned to one of the four groups according to the target Ce for the initial infusion of remifentanil using an Excel (Microsoft corp., Seoul, Korea) generated randomization table. The control group received normal saline (placebo) infused as if it was remifentanil to achieve a randomly chosen target Ce. The study groups received remifentanil to a target Ce of 2 ng ml^{-1} (Group R2), 4 ng ml^{-1} (Group R4), and 6 ng ml^{-1} (Group R6), respectively. The remifentanil (or saline) infusion was run until the pump indicated the target Ce had been achieved and then the TCI of propofol was started as described later.

The infusions of propofol and remifentanil were prepared using fresofol 2% inj., 50 ml vial (Fresenius Kabi, Austria) and Ultiva™ inj., 1 mg vial (GlaxoSmithKline, Belgium), respectively. Remifentanil 1 mg was diluted into 50 ml of normal saline (20 μg ml^{-1} solution). Both infusions were prepared in 50 ml syringes. To maintain blinding, in the control group, the remifentanil infusion was replaced with 50 ml of normal saline in 50 ml syringe. This was replaced by remifentanil-filled syringe after the pain assessment had been completed. A commercial TCI pump (Orchestra® Base Primea, Fresenius Vial, France) was used for the effect-site TCI of propofol and remifentanil. The pump used the Marsh and colleagues[12] and Minto and colleagues[13] models for propofol and remifentanil, respectively.

Blinding was maintained by the involvement of two practitioners at the induction of every patient: the TCI manipulator and the anaesthesia provider. The TCI manipulator prepared and controlled TCI pump and notified the anaesthesia provider of the start of remifentanil (or placebo) and propofol infusions. The anaesthesia provider assessed complications and pain and was unable to see or control the infusion pumps during induction of anaesthesia. Control of the TCI device was handed to the anaesthesia provider after induction, when data acquisition was complete.

Patients were not premedicated before they arrived in the operating room (OR). An 18 gauge venous cannula was placed in the forearm. Three three-way taps were connected to the cannula for infusion of remifentanil, propofol, and lactated Ringer's solution. Standard monitoring, including non-invasive arterial pressure, ECG, pulse oximetry, and capnography, was applied and assessed continuously until the end of induction. Oxygen was administered using a face mask during remifentanil (or placebo) infusion. Remifentanil-related complications were assessed by repeated observation and verbal questions until the target Ce of remifentanil was reached. These complications were categorized as major and minor. Major complications included hypotension (>20% decrease in arterial pressure compared with baseline value), bradycardia (heart rate <45 beats min^{-1}), chest wall rigidity (expressed as chest tightness and difficulty in breathing), and desaturation (Sp_{O_2}<95%). Minor complications included dizziness, nausea, cough, pruritus, and erythema. When the preset target Ce of remifentanil was reached, the Observer's Assessment of Alertness and Sedation (OAA/S) scale was checked to subjectively assess the level of consciousness to ensure adequate response to pain questionnaires.[14]

When the intended target Ce of remifentanil was reached (or 100 s after start of the saline infusion in the control group), TCI of propofol was then started at a target Ce of 3.4 μg ml^{-1}. Using the integrated Marsh model, a bolus of propofol was infused for 10 s and the infusion was then stopped to achieve peak effect (loss of consciousness) at 1.6 min. Pain from the propofol infusion was thus assessed during the 1 min period after the start of propofol infusion and before the patients lost consciousness. The severity of pain was assessed using a four-point scale. Pain manifest as a verbal response accompanied by facial grimacing or withdrawal of arm was scored as severe; grimacing or withdrawal not accompanied by a verbal response was scored as moderate pain. If severe or moderate pain was not observed within 30 s, the patient was asked whether they had any discomfort in the arms; if they answered 'yes', this was scored as mild pain; if they answered 'no', this was scored as no pain.[11]

After the pain assessment was finished, the saline syringe was replaced with a remifentanil infusion if necessary and the TCI device was adjusted to deliver target Ce of 3.4 μg ml^{-1} and 6 ng ml^{-1} of propofol and remifentanil, respectively. Control of the device was then handed over to the anaesthesia provider. The drug infusions were continued until the patient fell asleep and tracheal intubation was facilitated by rocuronium 0.6 mg kg^{-1}. The patients were mechanically ventilated with oxygen and air, and anaesthesia was maintained using TCI with both drugs and intermittent bolus injections of rocuronium.

Statistical analysis

From previous studies,[1] we expected the incidence of injection pain in the placebo group to be at least 70% and a reduction in the incidence of 40% with an effective Ce of remifentanil. Our study was powered to detect such a reduction with a type I error of 0.05 (two-tailed) and a desired power of 0.8. This required 29 patients per group (with Yate's correction). We assumed a dropout rate of 10% and so increased the sample size to 32 patients per group.

Differences in the incidence of propofol injection pain among the groups were analysed using the χ^2 test with the Bonferroni correction for multiple comparisons (P=0.05/3). Differences in the pain scores among the groups were analysed with the Kruskal–Wallis test. *Post hoc* comparisons were performed to detect any significant differences in pain scores among the groups. The concentration–effect relationship was examined with linear-by-linear association and Spearman's rho. The incidence of complications was examined with Fisher's exact test. Again a correction was made for multiple comparisons.

Numbers needed to treat (NNT) for each drug dose were calculated (the total number of patients you need to treat to prevent additional pain in one who would have had pain if they had received placebo pre-treatment).[15]

All values are expressed as mean (SD) or absolute numbers. A value of $P<0.05$ was considered significant. All statistical analyses were performed using SPSS software (version 12, SPSS Inc., IL, USA).

Results

Initially, 128 patients were enrolled into the study. One patient in Group R6 had hypoxaemia (Sp_{O_2}=92%) of undetermined cause on arrival in the OR and one patient in the control group fell asleep during the propofol infusion before the pain assessment was completed. These two patients were excluded from the statistical analyses; therefore, data are presented on 126 patients.

The four groups were similar with respect to patient characteristics (Table 1). Both the incidence and severity of pain were significantly different among the groups ($P<0.001$). As shown in Table 2, the incidence of pain was significantly reduced in Groups R4 and R6 compared with the control and R2 groups ($P<0.001$). A negative correlation between the remifentanil target Ce and the incidence of pain was found ($P<0.001$) by linear-by-linear association. However, there was no significant difference in pain incidence between R4 and R6 groups. The severity of pain was significantly less in Groups R4 and R6 compared with the control group and Group R2 ($P<0.001$). A negative correlation between remifentanil target Ce and severity of pain was also found ($r=-0.584$, $P<0.001$), although Group R4 was not significantly different from Group R6.

Table 1 Patient characteristics. Values are expressed as numbers of patients, mean (range), or mean (SD)

	Control	R2	R4	R6
Target Ce of remifentanil (ng ml^{-1})	0	2	4	6
Number of patients	31	32	32	31
Sex (M/F)	4/27	3/29	3/29	6/25
Age (yr)	51 (33–66)	48 (24–67)	46 (32–68)	46 (25–64)
Height (cm)	160 (7)	161 (7)	158 (7)	161 (7)
Weight (kg)	59 (9)	60 (9)	58 (9)	60 (7)

Table 2 Incidence and severity of pain. Values are expressed as numbers of patients. *$P<0.001$ for the incidence and the severity of pain, compared with both the control and R2 groups

	Control (n=31)	R2 (n=32)	R4* (n=32)	R6* (n=31)
Incidence	26	25	12	6
Severity (none/mild/moderate/severe)	5/9/7/10	7/6/12/7	20/8/4/0	25/6/0/0

Table 3 Incidence of complications. Values are expressed as numbers of patients. *Total numbers of minor complications are not consistent with the sum of incidences in R4 and R6 groups, because some complications occurred simultaneously in the same subject. †Minor complications were significantly less frequent in control group ($P<0.001$). However, incidences of minor complications in the three study groups were comparable with one another

	Control (n=31)	R2 (n=32)	R4 (n=32)	R6 (n=31)
Major complications				
Desaturation	0	0	0	0
Bradycardia	0	0	0	0
Hypotension	0	0	0	0
Chest wall rigidity	0	1	2	0
Total	0	1	2	0
Minor complications				
Dizziness	0	4	7	12
Nausea	0	0	1	0
Cough	0	1	2	4
Pruritus	0	0	0	0
Erythema	0	2	1	6
Total*	0†	7	9	14

For all subjects, OAA/S levels were 4 (lethargic response to name spoken in normal tone) and 5 (prompt response to name spoken in normal tone), indicating adequate responses to questionnaires.

Chest wall rigidity, a major complication, which was described as transient chest discomfort, was observed in one subject in Group R2 and two subjects in Group R4. This low incidence did not achieve statistical significance in a comparison between groups. Minor complications were significantly more frequent in Groups R2, R4, and R6 ($P<0.001$) compared with the control group, although incidence of complications was not significantly different between the three study groups (Table 3).

The NNT (95% CI) was 17.4 (−7.37 to 3.99), 2.16 (1.48–3.97), and 1.55 (1.20–2.20) for Groups R2, R4, and R6, respectively.

Discussion

A quantitative review of analgesic interventions to prevent propofol injection pain revealed i.v. lidocaine given with a venous tourniquet to be the most effective,[1] suggesting that local analgesic pre-treatment may be effective for propofol injection pain. However, this may not be true for opioids, because i.v. opioids given as Bier's block before propofol injection failed to show analgesic efficacy,[16 17] whereas there are several reports that systemic opioids relieved propofol injection pain.[7 8 18] These facts suggest that prevention of propofol injection pain by opioids may be largely mediated via central opioid receptors. However, the efficacy of systemic opioids was not as high as expected[1] because conventional weight-adjusted drug administration did not show a clear dose–response relationship.

The premise of effect-site modelling is that drug effect is the function of the drug concentration at the site of action.[19] This is applied clinically in the infusion of anaesthetic drugs targeted to a chosen Ce. In this study, we showed that remifentanil administered using an effect-site TCI could reduce the incidence and severity of propofol infusion pain in a concentration-related manner, without significant complications. However, the effect reached the limit at 4 ng ml^{-1} of remifentanil Ce because no more reduction in pain was observed at a target Ce of 6 ng ml^{-1} of remifentanil.

Remifentanil has an analgesic potency 20–30 times of alfentanil and a rapid onset time. The use of remifentanil to prevent the pain of propofol injection has been studied by several investigators. Roehm and colleagues[10] used a continuous infusion of remifentanil at a rate of 0.25 μg kg^{-1} min^{-1} more than 60 s before propofol injection and found that the incidence of propofol injection pain was reduced from 62% to 30%. Rahman Al-Refai and colleagues[20] showed that remifentanil doses of 0.25–0.5 μg kg^{-1} min^{-1} reduced propofol injection pain in 39% and 63% of children. Basaranoglu and colleagues[11] showed that remifentanil 0.25 μg kg^{-1} min^{-1} started 1 min before propofol injection was more effective (25% pain reduction) than that given just before propofol injection (9% pain reduction). The implication of these reports was that both an appropriate dose and time interval are important to produce the maximum effect of remifentanil pre-treatment on discomfort from propofol injection. However, it is difficult to establish the Ce of remifentanil at a certain time point when using a constant rate infusion. When given by continuous infusion, there is a slow increase in the plasma concentration of remifentanil yielding an even slower increase in the Ce of remifentanil. Thus, an effective Ce cannot be achieved within the limited time available during induction.

We were concerned that increasing the remifentanil target Ce might produce opioid-related complications. TCI targeting effect-site concentrations are more prone to cause complications because they permit an overshoot of the plasma drug concentration to achieve the target Ce rapidly.[21] Fortunately, our results showed that even at a target Ce of 6 ng ml^{-1} (to achieve this target concentration, the plasma concentration of remifentanil reaches about 18 ng ml^{-1}), critical complications such as desaturation, hypotension, and bradycardia were not observed in our ASA I–II patients. Although chest wall rigidity was suspected in three patients, it was described as mild and transient chest discomfort by the patients and did not result in problems. Such chest discomfort could be categorized as a minor problem. However, careful monitoring and supplemental oxygen would be critical for the older and debilitated patients.[22]

The current study has two limitations arising from the study design. We used propofol 2% solution rather than the propofol 1% used in other studies. Concerns about the large lipid load associated with a prolonged propofol infusion have led to the use of modified formulations of propofol.[23] However, there is no study that compared the frequency and intensity of propofol pain between 1% and 2% solutions. Song and colleagues[24] reported that Ampofol® (a new lower-lipid formulation of propofol containing propofol 1% and 50% reduced soybean oil) caused more pain than generic propofol 1% and suggested that this might be related to increased free aqueous portion of propofol. It may be inferred that propofol 2% containing relatively less fat and subsequently more aqueous propofol might produce more injection pain than propofol 1%. This fact may contribute to the higher incidence of pain in our control group compared with those of previous studies. The other limitation was that we did not use higher doses of remifentanil for our study. Our result demonstrated positive relationships between the target concentrations of remifentanil and pain reduction ($P<0.001$ for both incidence and severity of pain). Higher remifentanil target Ce would possibly produce further reductions in propofol injection pain. However, in our experience, an effect-site concentration of remifentanil of more than 6 ng ml^{-1} is rarely required during induction of anaesthesia using TCI. In view of the synergism between propofol and remifentanil, a future study with higher remifentanil effect-site concentrations and a reduced propofol dose may show further reductions in injection pain. This will be of clinical benefit if it is not associated with an increase in the incidence of complications.

In conclusion, we showed that during induction of anaesthesia with propofol and remifentanil TCI, prior administration of remifentanil at a target Ce of 4 ng ml^{-1} reduces the frequency and intensity of pain from the propofol infusion and is safe. This method may provide the patient's comfort at the expense of spending another 100 s during induction.

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