

Role of Tramadol in Reducing Pain on Propofol Injection

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ABSTRACT

Propofol is frequently associated with pain on injection. We evaluated the effect of tramadol in a randomised, double-blind study using a tourniquet venous retention technique. Normal saline placebo was given intravenously to patients in Group 1 (n = 30), tramadol 50 mg to Group 2 (n = 30), and lignocaine 50 mg to Group 3 (n = 30). The venous retention of drugs was maintained for 1 minute, followed by tourniquet release and intravenous administration of propofol. Pain assessment was made immediately after propofol injection. There was a significant reduction in the incidence of pain associated with propofol administration in patients pretreated with lignocaine and tramadol ($P < 0.05$). In addition, pretreatment with tramadol was as effective as lignocaine in reducing pain on propofol injection.

Keywords: Anaesthetics, Intravenous: Propofol, Narcotics: Tramadol, Anaesthesia, Complications: pain

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INTRODUCTION

It is well-known that intravenous injection of propofol is associated with pain. The incidence ranges from 28% to 90%⁽¹⁾ and may be recalled as an unpleasant experience by the patient. Many methods have been used to reduce the incidence and severity of this complication with varying success rates⁽²⁾. Tramadol is a centrally acting weak mu-receptor agonist and inhibits noradrenaline re-uptake as well as promotes serotonin release⁽³⁾. We postulate that it may have a peripheral action on the free nerve endings of blood vessels⁽⁴⁾ and proceeded to evaluate its efficacy, in conjunction with temporary venous occlusion, in reducing pain on injection of propofol.

PATIENTS AND METHODS

A randomised, double-blind controlled study involving 90 unpremedicated patients of ASA I - II status aged

between 18 and 60-years-old was conducted with ethics committee approval and patients' informed consent. The patients were randomly selected using a coded syringe method into three groups of 30 each. Group 1 received 5 mls of normal saline as placebo. Group 2 received 5 mls (50 mg) of tramadol as the test drug while Group 3 was administered 5 mls (50 mg) of lignocaine. A 22 G Venflon cannula was inserted into the largest vein on the dorsum of the non-dominant hand without lignocaine infiltration.

The patient's arm was elevated for 30 seconds before a tourniquet was applied at the forearm inflated to 50 mmHg above baseline systolic pressure. The study drug was injected and the occlusion released one minute later. Propofol calculated at 2.5mg kg⁻¹ was then administered as a bolus dose over 30 seconds.

The patients were informed of the possibility of a 'burning sensation' in the forearm during induction of anaesthesia and were requested to grade the severity of pain as none, mild or severe at 10 seconds interval. Limb withdrawal and grimacing were taken to be signs of severe pain. In the recovery room, the patients were asked if they could recall any pain at the time of induction and to grade it. Upon loss of consciousness, anaesthesia continued as planned.

Post-operatively, all cases of pain and usage of analgesics in the recovery area as well as patients' ability to recall any pain on direct questioning were recorded. Demographic data between the three groups were compared using ANOVA. Chi-square test was used to compare the incidence of pain in the three groups. Results were considered significant when $p < 0.05$. Power analysis showed that 84 patients were required for a power of 90% at $p < 0.05$ for a reduction of pain incidence from 80% to 40%.

RESULTS

Analysis of the three groups did not show any differences in age, sex or weight (Table I). The incidence of pain was 30% in the tramadol group as compared to 27% in the lignocaine group and 83% in the placebo group (Table II) ($P < 0.001$, placebo vs lignocaine and tramadol). There is no significant

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Table I. Demographic data: Values are expressed as mean (SD)

	Placebo (n = 30)	tramadol (n = 30)	lignocaine (n = 30)
Age (yrs)	39.3 (15.8)	37.4 (15.1)	36.2 (12.9)
Sex (M : F)	14 : 16	15 : 15	17 : 13
Weight (kg)	59.9 (10.1)	64.1 (12.4)	65.2 (10.5)

Table II. Incidence and grade of pain on propofol injection

	Results expressed as number (%)		
	Placebo (n = 30)	tramadol (n = 30)	lignocaine (n = 30)
None	5 (17)	21 (70)*	22 (73)*
Mild	12 (40)	8 (27)	8 (27)
Severe	13 (43)	1 (3)*	0 (0)*

* P<0.05 compared to placebo.

difference in the incidence of pain between the tramadol and lignocaine groups. Severe pain occurred in 13 patients in the control group as compared to one in the tramadol and nil in the lignocaine group (Table II). Post-operative recall of pain was 80% in the control group, 44% in the tramadol and 37% in the lignocaine group.

DISCUSSION

The mechanisms of pain when propofol is given intravenously have been postulated to be due to either a direct irritant effect giving rise to an immediate sensation of pain or an indirect effect via the release of mediators leading to a delayed onset. The latter theory involves the release of kininogens when propofol comes into contact with the vascular endothelium⁽⁵⁾. Furthermore, Klement and Arndt⁽⁶⁾ postulated that the afferent free nerve endings between the media and intima are the sensors for this pathway.

Opioid receptors are found in the dorsal root-ganglia, the central terminals of primary afferent nerves^(7,8) and peripheral sensory nerve fibres and their terminals⁽⁹⁾. Endogenous or exogenous opioids after activating those receptors will increase potassium currents and decrease calcium currents in sensory neuron cell bodies leading to inhibition of signal transmission⁽¹⁰⁾. Opioids can also inhibit the release of excitatory and proinflammatory compounds from sensory nerve endings⁽¹¹⁾.

With the above proposed mechanisms in mind, various authors have tried different pharmacological agents and methodologies to decrease the incidence and severity of pain including the use of lignocaine and tourniquet⁽¹²⁾, opioids^(13,14) and different sites of injection⁽¹⁵⁾.

Lignocaine has been shown to be successful especially when used with a tourniquet. Mangar and Holak⁽¹²⁾ found that lignocaine given after a tourniquet was inflated to 50 mmHg virtually abolishes this pain.

Trials with opioids such as fentanyl, alfentanil and pethidine however showed mixed results. Fletcher et al⁽¹⁶⁾ found that intravenous alfentanil 1 mg given 15 seconds before administration of propofol was efficacious in reducing the incidence and severity of pain. Similarly, Nathanson et al⁽¹³⁾ demonstrated that the incidence of pain was reduced with alfentanil (24%) compared to placebo (67%). However, Wrench et al⁽¹⁴⁾ failed to show any peripheral action by alfentanil in reducing pain and concluded that there was no difference between placebo and the study drug. These authors used a tourniquet with cuff pressure of 50 mmHg above arterial pressure for 30 seconds together with intravenous alfentanil. The amount of propofol used on per kg basis was similar to our study. While the differences between this study and ours lie in the study drug (tramadol vs alfentanil) and the time of tourniquet applied (1 minute versus 30 seconds), we felt that the longer time allowed for tramadol to act locally on the peripheral opioid receptors may have succeeded in inhibiting pain signal transmission from the free nerve endings in the vascular endothelium.

Not only is tramadol effective in attenuating pain on propofol injection, we feel that it is also useful for intra and post-operative analgesia when relatively minor operations are undertaken. Nine patients in the tramadol group underwent cone biopsy, dilation and curettage or hysteroscopic procedures but only one needed additional analgesics post-operatively. Tramadol has the same analgesic potency as pethidine and 1/10 that of morphine. In patients who had undergone hysterectomy, it was demonstrated that i.v. tramadol 50 mg was as effective as i.v. morphine 5 mg in treating moderate pain⁽¹⁷⁾. In another study comparing i.v. tramadol and epidural morphine for post thoracotomy analgesia, the two methods were found to be equally effective⁽¹⁸⁾. It may be useful to increase the dose of i.v. tramadol from 50 to 100 mg in future studies to determine if there is a further reduction in perioperative analgesic needs and if the number of patients complaining of propofol induced pain will be decreased. There were yet no reports of clinically relevant respiratory depression as a result of treatment with tramadol. Vickers et al⁽¹⁹⁾ compared patients breathing spontaneously under general anaesthesia when given i.v. tramadol 0.5 - 2 mg kg⁻¹ versus i.v. morphine 0.143 mg kg⁻¹. It was found that apnea or clinically relevant respiratory depression was present in those given morphine but none with

tramadol. It was thus not surprising that there were no episodes of apnea detected in our patients given tramadol. Interestingly, although tramadol has not been reported to cause histamine release, one patient in our study developed urticaria and itchiness localised to the forearm after it was injected with tramadol.

One problem that we encountered in this study was that of discomfort in the forearm during the period of tourniquet though it had only occurred in less than 5% of the patients. This may be avoided if a simple tourniquet with a Vacro strap is used instead of one using a sphygmomanometer pumped to 50 mmHg above systolic pressure.

The data on recall of pain shows that a greater percentage of patients who received placebo had recall of pain during the recovery period. Seven of the 12 patients in the placebo group who reported mild pain had recall compared to three in eight for the patients given tramadol. All 13 who complained of severe pain in the former and the sole patient who had severe pain in the latter did remember the unpleasant experience.

There have been many studies done with various pharmacological and non-pharmacological means to reduce the incidence of pain on propofol injection. The most effective method appears to be that of lignocaine with an application of a tourniquet. This method however does not provide for any perioperative analgesia for the patient. We have found intravenous tramadol to be equally effective in relieving pain associated with propofol injection compared to lignocaine in addition to the possibility of it providing good analgesia for mild to moderate perioperative pain as evidenced by previous studies^(17,18).

CONCLUSION

In conclusion, we have found tramadol to have a peripheral site of action and it is as effective as lignocaine in reducing the incidence and severity of pain on propofol injection. Future studies with different doses of tramadol may be useful to determine if there is a dose-dependent effect on the incidence and severity of pain on propofol injections as well as perioperative pain relief.

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