Comparison of target controlled infusion and total intravenous anaesthesia with propofol and remifentanil for lumbar microdiscectomy

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ABSTRACT

Background. Propofol is often combined with remifentanil for induction and maintenance of total intravenous anaesthesia. Target-controlled infusion (TCI) permits adapting infusion to pharmacokinetic models. In this study we compared depth of anaesthesia, haemodynamic variables and times to recovery in patients scheduled for lumbar microdiscectomy and receiving either manually controlled (group I) or target-controlled (group II) infusion of propofol and remifentanil for anaesthesia.

Methods. Twenty three patients (group I) received a bolus induction of propofol 2 mg kg⁻¹ and remifentanil 1 µg kg⁻¹. Twenty five patients (group II) received propofol and remifentanil at an initial effect site concentration of 4 µg mL⁻¹ and 4 ng mL⁻¹ respectively. According to BIS and haemodynamics, propofol/remifentanil infusion rates (group I) or concentration of propofol/remifentanil at an effect-site were adjusted upwards or downwards. We monitored bispectral index (BIS), mean arterial pressure (MAP) and heart rate (HR) during subsequent stages of anaesthesia and operation (T1–T10).

Results. Induction and total doses of propofol and remifentanil, times to recovery were comparable in both groups. BIS was lower at T2–T10 in comparison to baseline values. At T4 and T5 BIS was lower in group II than in group I. In group I, mean HR values were lower at T7–T9 in comparison to baseline values. In exection of MAP at T6 in group II, MAP was lower at T2–T9 in comparison to baseline values in both groups.

Conclusion. There are no clinically important differences in haemodynamic variables, depth of anaesthesia, time to recovery and doses of propofol/remifentanil between manually controlled and target-controlled infusion of propofol and remifentanil.

Key words: target controlled infusion, propofol, remifentanil

Propofol, a short-acting intravenous anaesthetic, is used for both the induction and maintenance of anaesthesia due to its quick distribution, metabolism and excretion; moreover, it does not accumulate markedly even during long-term continuous infusions [1]. Remifentanil is a synthetic opioid receptor μ₁ agonist with rapid onset of action and ultra-short analgesic potency, irrespective of the dose and duration of administration [2]. Thanks to such characteristics, the level of analgesia can be accurately controlled. The unique properties of remifentanil are mainly attributable to extremely quick breakdown by non-specific esterases in blood and tissues [2]. Since the drug effects disappear almost instantly once its infusion has been discontinued, patients have to be protected against pain sensations in the immediate postoperative period [2].

The beneficial pharmacokinetic characteristics of propofol and remifentanil enable their combined use in total intravenous anaesthesia, which is increasingly common in various surgical procedures [3, 4, 5, 6, 7].

Propofol and remifentanil can be administered in the traditional manually controlled way, when the anaesthesiologist...
adjusts the speed of administration through the infusion pump. Recently, target controlled infusion (TCI) systems have become widely available, in which once the required concentration in the serum or effector organ (the brain) is programmed, the infusion pump adjusts the infusion speed based on the algorithm involving gender, age, body weight, and height [1]. The administration of propofol and remifentanil using TCI ensures quick provision and maintenance of appropriately deep anaesthesia and analgesia [1, 8, 9].

The aim of the present study was to compare target controlled infusion and total intravenous anaesthesia with propofol and remifentanil based on selected hemodynamic parameters, drug requirements and times to recovery.

METHODS

The study design was approved by the Bioethics Committee of the Medical University of Gdańsk. Forty-eight ASA I and II patients scheduled for lumbar microdiscectomy were enrolled. The exclusion criteria were obesity, cardiovascular diseases, diabetes mellitus, renal and hepatic failure, medications likely to affect the parameters monitored, alcohol or drug abuse, tobacco smoking, and proven hypersensitivity to the agents used during anaesthesia. The procedures were carried out in the morning hours. Patients were premedicated with oral midazolam, 0.2 mg kg b.w.-1 45 min before anaesthesia. In the operating theatre, each patient was inserted two cannulae Ø 1.3 mm to the antebrachial veins and 6 ml kg b.w.-1 of the Ringer’s solution were transfused within 15 min. Before the induction of anaesthesia, the 5-minute preoxygenation was used. The Perfusor Space infusion pumps (B. Braun Melsungen, Germany) equipped with the Dash 3000 monitor (GE Medical Systems, USA) and Vamos gas monitor (Dräger, Germany), maintaining ETCO₂ within the range of 37–40 mm Hg.

The infusion of propofol during the procedure was adjusted to the bispectral index (BIS AspectMedical Monitoring, USA) of 35–55. If required, the speed of flow was changed by 0.5 mg kg b.w.-1 h⁻¹ in group I or the target drug concentration by 0.5 μg kg b.w.-1 in group II. Remifentanil was infused to ensure haemodynamic stability, i.e. haemodynamic parameters could not change by more than 20% compared to baseline values. The speed of flow was altered by 0.025 μg kg b.w.-1 min⁻¹ in group I or the target remifentanil level by 0.5 ng kg b.w.-1 in group II, if need be. The target concentration and speed of drug flow were changed at 5-minute (not shorter) intervals. The infusion of propofol and remifentanil was discontinued when the final skin suture was applied.

The heart rate (HR), mean arterial pressure (MAP) and bispectral index (BIS) were monitored at the following measurements times points: T₀ — onset of the study, T₁ — 1 min after administration of drugs, T₂ — after administration of the total dose of propofol and remifentanil, T₃ — intubation, T₄ — 1 min after intubation, T₅ — 2 min after intubation, T₆ — skin incision, T₇ — approaching the disc, T₈ — removal of the disc, T₉ — skin suture, T₁₀ — extubation.

Moreover, the following times were recorded: return of spontaneous respiration with TV ≥ 4 ml kg b.w.-1, extubation, eye opening to verbal command and spontaneous eye opening.

Data were statistically analysed using Statistica 0.1 software (StatSoft Inc. Tulsa, USA) and GraphPad InStat ver. 3.0 programme (GraphPad Software Inc., USA) and expressed as a mean ± SD. Data distribution was tested using the Kolmogorov-Smirnov test. For intra-group comparisons the Dunnett’s test was used; for intergroup comparisons, the Mann-Whitney U test was applied. P < 0.05 was considered statistically significant.

RESULTS

The characteristics of patients in both groups were presented in Table 1. The mean durations of anaesthesia were comparable.

In both groups, the mean BIS values at individual measurement points were lower compared to baseline values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>16/7</td>
<td>17/8</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>44.4 ± 13.0</td>
<td>47.9 ± 11.4</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>72.8 ± 13.0</td>
<td>76.0 ± 13.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.0 ± 0.1</td>
<td>171.0 ± 0.1</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>103.4 ± 21.0</td>
<td>109.3 ± 28.1</td>
</tr>
</tbody>
</table>
At T4 and T5, the mean BIS values in group I were higher than in group II (Fig. 1).

In group I, the mean HR values were lower than the baseline values at T7, T8 and T9 (Fig. 2). In both groups, the MAP values were lower than the baseline ones at all measurement points (except for T6 in group II) (Fig. 3).

The data concerning the propofol and remifentanil infusion at individual anaesthesia stages in group I and II were presented in Table 2 and 3, respectively. The doses of propofol and remifentanil used for induction and maintenance were comparable in both groups (Fig. 4).

Patients did not receive additional rocuronium doses during the procedure and reversal of neuromuscular block was not necessary as TOF ratio at completion of anaesthesia was ≥ 0.9.

The times between surgery completion and return of respiration, extubation, eye opening to verbal command,
as well as spontaneous eye opening were comparable in both groups (Fig. 5).

**DISCUSSION**

In everyday anaesthetic practice, propofol is one of the most commonly applied synthetic opioids. The combination of the anaesthetic and analgesic, often together with a non-depolarising neuromuscular blocker, is widely used for total intravenous anaesthesia [10].

Opioids, remifentanil in particular, reduce the propofol requirements during induction and maintenance of anaesthesia [10, 11]. During induction with propofol, remifentanil diminishes or eliminates the endotracheal intubation-associated BIS increase [12]. Moreover, it decreases the intubation effects on auditory evoked potentials [13]. In a dose-dependent manner, remifentanil weakens the cardiovascular responses to pain stimuli [10, 12, 13]. A single dose of remifentanil induces quick, ultra-short action; therefore, it is ideal before short-term pain stimuli, such as intubation [13]. Furthermore, its pharmacokinetic properties ensure precise control of analgesia during surgery and guarantee quick subsidence of its effects.

The TCI systems enabling accurate dosing of propofol and remifentanil for induction and maintenance of anaesthesia have been available for several years. During our study, the effect-site concentrations of propofol and remifentanil were set according to the Schnider’s algorithm and Minto equation, respectively. Compared to the target...
serum concentration, the target effect-site concentration is better correlated with the depth of anaesthesia [8, 9].

When administered alone, propofol causes loss of consciousness in 50% of anaesthetised patients at its serum concentration of 3.4 µg mL⁻¹ [10, 11] and in 90% at the concentration of 4 µg mL⁻¹ [12]. However, the doses of propofol blocking the responses to nociceptive stimulation, e.g. related to laryngoscopy, intubation or surgery, are markedly higher [10, 11]. According to the study carried out by Iannuzzi and co-workers, in which BIS and the modified observer’s assessment of alertness/sedation scale were used, propofol administered according to the Schnider’s method caused the loss of verbal contact at the brain concentration ≥ 3.5 µg mL⁻¹ and BIS ≤ 62, whereas the level ≥ 5.5 µg mL⁻¹ induced complete unresponsiveness and BIS reduction to 39 [14]. In our study, the target propofol concentration

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**Figure 4.** Induction and total doses of propofol and remifentanil (X and SDs)

**Figure 5.** Times to respiration return with TV ≥ 4 ml kg⁻¹, extubation, eye opening to command, and spontaneous eye opening (X and SDs)
used before intubation (4 µg mL⁻¹) decreased BIS in the similar way as in the manually controlled infusion group, where the total dose was 2 mg kg⁻¹, which is considered appropriate for induction of anaesthesia [15].

It is known that consciousness is regained when the serum level of propofol decreases to 3.4–1.8 µg mL⁻¹ [3, 11]. According to Mertens and colleagues [11], in non-premedicated patients anaesthetised for abdominal surgical procedures, the target serum concentration of propofol should be maintained above 2 µg mL⁻¹ at the target concentration of remifentanil ≥ 4 ng mL⁻¹. In our patients, the target concentration of propofol was higher than 2 µg mL⁻¹, yet only at the effect site. The target levels of remifentanil were lower than recommended by Mertens and colleagues. The differences are likely to result from premedication used in our patients, less severe pain stimulation during microdiscectomy and the different algorithm applied.

In our study, BIS was maintained within the range of 35–55, considered sufficient to maintain "surgical sleep" [7, 15]. In group I, the BIS values increased immediately after intubation, which was not observed in group II. This might have been associated with the protocol of propofol administration. In the group with drugs administered traditionally, most of the propofol dose (1.5 mg kg b.w.⁻¹) was given within 30 sec and the continuous infusion was started after intubation. Thus, the value of BIS in this group was higher than in TCI group, in which propofol was administered continuously to achieve its serum level of 4 µg mL⁻¹ during intubation with relatively high levels maintained immediately after intubation.

The combination of propofol with opioids results in a decrease in the propofol concentration administered in TCI required for loss and regain of consciousness [10, 11]. The laryngeal mask airway can be effectively inserted without a relaxant in 50% of patients anaesthetised with propofol and remifentanil via TCI when their effect-site concentrations are 3.5 µg mL⁻¹ and 3.04 ng mL⁻¹, respectively [5]. In another study, the stable bispectral index was maintained between 40 and 50 when propofol was infused using the Marsh model to achieve its serum concentration of 3.4 µg mL⁻¹. To prevent stimulation of the sympathetic system during intubation and skin incision, the authors used the infusion of remifentanil to reach its effect-site levels of 5 and 2.1 ng mL⁻¹ [7]. In our TCI group, the programmed target concentration of remifentanil before intubation was 4 ng mL⁻¹, which is considered appropriate for intubation and equals the dose of 1 µg kg⁻¹ used in the manually controlled infusion of anaesthetics [4, 12, 16].

Our findings did not demonstrate any inter-group differences in the doses of propofol used for induction and in the total doses, which is consistent with the results published by other authors [16, 17]. However, some authors noted higher anaesthetic requirements in target controlled infusion compared to total intravenous anaesthesia [18, 19]. In the study by Breslin and co-workers [18], higher requirements resulted from higher doses of propofol administered over the first 30 min of TCI as the Marsh model was used, i.e. the target concentration of 5 µg mL⁻¹ during induction of anaesthesia. In this strategy, a higher total dose of propofol is required than using the Schnider’s algorithm, applied in our study [1]. Moreover, the studies mentioned above showed lower BIS values in the TCI group compared to our findings. Despite higher propofol requirements, their results did not demonstrate differences in recovery times or haemodynamic parameters between the TCI and manually controlled anaesthesia groups.

Irrespective of the intravenous anaesthesia method used, the times between the completion of remifentanil and propofol infusion and return of respiration, extubation, eye opening to command or spontaneous eye opening were comparable in both groups. Similar results were reported by some other authors [17, 18]. Otherwise, according to Grundmann and colleagues [6], the times of respiration return, extubation and eye opening in patients anaesthetised with propofol and remifentanil for discectomy were shorter, which can be associated with substantially lower doses of propofol (2 mg kg⁻¹ h⁻¹) and slightly higher doses of remifentanil (0.25 mg kg⁻¹ h⁻¹) used by them as compared to our study. It was demonstrated that recovery times after medium-long procedures, such as lumbar discectomy, depend mainly on the total propofol dose rather than the remifentanil dose [10].

During our study, mean arterial pressure values at individual measurement points were lower than the baseline values in both groups (except for skin incision in group II). A decrease in arterial pressure is more common after combined administration of propofol and remifentanil [4, 12, 17]. In the TCI group, the MAP values returned to those similar to baseline ones on skin incision, which is likely to result from too late action (in relation to a pain stimulus) or too low target concentration of remifentanil (2.2 ng mL⁻¹ on average). At the values observed, patients are considered haemodynamically stable (differences in cardiovascular parameters not higher than 20% of baseline values). In both groups, after induction and immediately after intubation, the decrease in MAP slightly exceeded 20% of baseline values, which resulted from the induction doses of propofol and remifentanil. Intravenous administration of short-acting and potent agents is associated with such benefits as anaesthesia control but also with the risk of sudden cardiovascular adverse events or other side effects, e.g. apnoea and muscle rigidity. Post-induction MAP reductions, particularly in the elderly or patients with cardiovascular diseases, can be prevented by decreasing the doses of anaesthetics.
or administering them in TCI, gradually increasing their concentration [4, 17]. Moreover, the TCI system, enabling us to enter the patient’s age and automatically adjust the doses (e.g. the Schneider’s model), may be essential [17]. Compared to target serum concentration, the use of target concentration in the brain was shown to result in quicker clinical effects without increased risks of hypotension [8, 9]. Passot and co-workers [17] demonstrated better haemodynamic stability of patients > 80 years of age anaesthetised using TCI compared to the manually controlled infusion of propofol. The MAP differences in the TCI group were 15% and 30% of baseline values, respectively for over 60% and 80% of the total anaesthesia time. In manually controlled infusions, it was 30% and 60% of this time. In our TCI group, MAP values increased since the moment of approaching the disc until skin suturing, yet remained within the range of 20% of baseline values in both groups. Additionally, the authors mentioned earlier demonstrated higher requirements of ephedrine, higher numbers of manoeuvres to correct the doses to maintain haemodynamic stability and the highest MAP decrease in relation to the baseline values in manually anaesthetized patients [17]. In our study, the requirements for propofol and remifentanil were comparable in both groups and there were no significant inter-group differences in haemodynamic parameters. Interestingly, in another study, despite higher propofol requirements in TCI anaesthetised patients, their haemodynamic parameters and recovery times did not differ from those observed in the manually anaesthetized patients [19].

In the manually controlled infusion group, mean HR values were lower compared to baseline values since the moment of approaching the disc until skin suturing; however, the decreases by more than 20% of the baseline were not observed.

CONCLUSION

There are no clinically significant differences in haemodynamic parameters, depth of anaesthesia, recovery times and anaesthetic requirements between target- and manually controlled infusions.

References:


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