Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by bispectral index


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**Background.** Interest in combining local and general anaesthesia has lead to studies investigating possible interactions. In a prospective, randomized, double-blind study, we tested whether local anaesthetics administered i.m. potentiate the hypnotic effect of propofol.

**Methods.** Sixty patients (three groups, n=20) undergoing lower abdominal surgery with total i.v. propofol anaesthesia were investigated. Patients in Group B received i.m. bupivacaine (5 mg ml⁻¹ 1 mg kg⁻¹), patients in Group L received i.m. lidocaine (100 mg ml⁻¹) 2 mg kg⁻¹ and patients in Group C received i.m. saline 5 ml before operation. Hypnosis was measured with bispectral index (BIS).

**Results.** The induction (BIS <45), and the maintenance doses of propofol (BIS between 40 and 50) were significantly less in Group B and Group L compared with the control group. Induction doses were 1.58 (SD 0.39), 1.56 (0.24) and 2.03 (0.33) mg kg⁻¹ respectively; P<0.0001. Maintenance doses were 6.33 (2.06), 7.08 (1.23) and 9.95 (2.02) mg kg⁻¹ respectively in the first hour; P<0.0001. Groups B and L were associated with an attenuated haemodynamic response to both induction and intubation.

**Conclusion.** I.M. administered local anaesthetics are associated with a decrease in both the induction and maintenance doses of propofol during total i.v. anaesthesia and a reduction in haemodynamic responses.

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The growing interest in combining local and general anaesthesia has led to studies investigating possible interactions between general anaesthetics and local anaesthetics administered via either spinal,¹ epidural,² ³ i.v.⁴ or i.m.⁵ ⁶ route.

In previous studies it has been shown that i.m. administration of either lidocaine or bupivacaine enhances the hypnotic effects of i.v. thiopental⁷ and propofol.⁶ However, these studies only concluded that local anaesthetics administered i.m. can reduce the induction dose of i.v. general anaesthetics, no evaluation of the effect of systemically used local anaesthetics on the maintenance dose of the general anaesthetic was carried out. Additionally, the results of both studies were based on responses to verbal commands. More reliable results can be obtained using bispectral index (BIS), which has been shown to be a specific and sensitive monitor of the hypnotic component of anaesthesia.⁷ In a prospecive, randomized, double-blind study, we investigated whether lidocaine or bupivacaine administered i.m. reduces the induction and the maintenance dose of propofol during BIS-guided total i.v. anaesthesia (TIVA).

**Methods**

With informed patient consent and approval from the ethical committee of the faculty, we studied 60 patients, aged 20–50 yr, ASA I or II, weighing 50–80 kg, undergoing minor elective lower abdominal surgery expected to last ≥1 h. To detect a decrease of 0.35 mg kg⁻¹ of the induction dose of propofol (accepting an alpha error of 5% and a beta
error of 10%), the required study size was 16 patients per group. Patients taking cardiovascular medication, with known hypersensitivity to local anaesthetics, neurological disorders, hypertension, baseline systolic arterial pressure (SAP) <100 mm Hg, heart rate (HR) <55 beat min⁻¹, or any serious medical conditions that would interfere with cardiovascular response assessment were excluded.

Patients did not receive premedication. They were prehydrated with NaCl 0.9% 500 ml solution, and were connected to an electrocardiograph monitor, automatic arterial pressure cuff and a pulse oximeter (Horizon 2000, Mennen Medical, Rehovot, Israel). BIS was monitored using a BIS sensor (Aspect Medical Systems, Natick, MA, USA) applied to the forehead as described by the manufacturer (BIS monitor Model A-2000™, Aspect Medical Systems, Natick, MA, USA). Patients were then allocated randomly to one of three groups according to a sealed envelope technique in a double-blind manner. In Group B, 20 patients received i.m. bupivacaine (5 mg ml⁻¹) 1 mg kg⁻¹ (Marcaine 0.5% flk AstraZeneca İlçə AŞ, Istanbul, Turkey), administered into the gluteus muscle 30 min before induction of anaesthesia. In Group L, 20 patients received i.m. lidocaine (100 mg ml⁻¹) 2 mg kg⁻¹ (Atrimal 10% ampul, Biosel İlçə AŞ, Istanbul, Turkey), administered into the gluteus muscle 10 min before induction of anaesthesia. In Group C, 20 patients served as controls and received i.m. saline 5 ml into the gluteus muscle 10 min before induction of anaesthesia. All i.m. injections were performed by an independent practitioner. HR, mean arterial pressure (MAP) and BIS values were recorded at t₀ (before i.m. administration), t₁ (before induction of anaesthesia), t₂ (after induction of anaesthesia) and t₃ (after intubation).

After a bolus dose of fentanyl 1.5 μg kg⁻¹ i.v., a physician, who was blinded to the dose or type of local anaesthetic (or saline) administered earlier, injected propofol 10 mg (1 ml) in 5 s every 15 s until the BIS score fell below 45. The total dose of propofol required to achieve a BIS below 45 was recorded in mg kg⁻¹. When BIS <45, the total dose of propofol required to achieve a BIS score between 40 and 50. When the BIS score was out of these limits for ≥10 s the dose of propofol was changed by 1 mg kg⁻¹ h⁻¹ every 20 s. The total maintenance dose of propofol during the first hour of anaesthesia was recorded in mg kg⁻¹ h⁻¹.

Inadequate analgesia was defined as response to surgical stimuli by hypertension (SAP >20% above preoperative baseline value for >5 min) or tachycardia (HR >20% above preoperative baseline value), while BIS level was between 40 and 50. In cases of inadequate analgesia, patients were given bolus doses of remifentanil 0.5 μg kg⁻¹. If this treatment was unsuccessful, the remifentanil infusion rate was doubled.

Bradycardia was defined as HR <40 beat min⁻¹ and hypotension as a decrease in SAP >20% of the baseline value. Hypotension was treated by infusion of lactated Ringer’s solution 3–5 ml kg⁻¹, and if necessary, with ephedrine 5 mg i.v. Bradycardia was treated with atropine 0.5 mg i.v. The frequency of hypotension, bradycardia and inadequate analgesia and supplemental remifentanil doses was recorded.

To assess intraoperative awareness, a number was repetitively recited to each patient four times during anaesthesia at 5, 10, 15 and 20 min. The patients were specifically questioned for recall of this number.

Analysis of variance (ANOVA) was used to evaluate the differences in patient characteristics, HR, MAP, BIS-values, and propofol doses for induction and maintenance between the groups. Data at different times within the groups were compared with a repeated measures ANOVA (GraphPad InStat™, GraphPad Software V2.02). The alterations in HR and MAP after the induction and intubation were also compared in the three groups. To compare the frequency of hypotension, bradycardia and inadequate analgesia, an appropriate χ²-test was used. P<0.05 was regarded as statistically significant.

Results

There were no statistically significant differences with respect to patient characteristics between the groups (Table 1). Propofol doses required for the induction of anaesthesia were significantly less in patients in Groups B and L compared with the control group (P<0.0001; 1.58 (0.39), 1.56 (0.24) and 2.03 (0.33) mg kg⁻¹, respectively; P<0.01 between Groups B and C, and between Groups L and C, Fig. 1). The maintenance doses for the first hour of surgery were also significantly less in these patients (P<0.0001; 6.33 (2.06), 7.08 (1.23) and 9.95 (2.02) mg kg⁻¹ h⁻¹ respectively; P<0.01 between Groups B and C, and between Groups L and C, Fig. 2). There was no statistical difference between Groups B and L regarding the induction and maintenance doses of propofol.

HR and MAP values are shown in Tables 2 and 3. HR was decreased after induction by 13.7 (6.2), 14.0 (5.8), 14.5 (4.6)% in patients receiving bupivacaine, lidocaine and

**Table 1** Patient characteristics, mean (SD) [range]. No significant differences

<table>
<thead>
<tr>
<th>Group</th>
<th>n=20</th>
<th>Gender (F/M)</th>
<th>Age (yr) [21–50]</th>
<th>Weight (kg) [67.8 ±7.8]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B</td>
<td></td>
<td>7/13</td>
<td>37.6 [21–50]</td>
<td>67.8 (7.8)</td>
</tr>
<tr>
<td>Group L</td>
<td></td>
<td>8/12</td>
<td>38.5 [23–49]</td>
<td>66.7 (6.3)</td>
</tr>
<tr>
<td>Group C</td>
<td></td>
<td>6/14</td>
<td>37.6 [20–48]</td>
<td>65.5 (7.7)</td>
</tr>
</tbody>
</table>
The increase in HR after intubation was statistically different between the groups ($P=0.0003$; 11.8 (7.9), 16.1 (9.9) and 25.5 (12.3)% in Groups B, L and C, respectively; $P<0.001$ between Groups B and C, $P<0.05$ between Groups L and C).

Regarding the MAP, the decrease after induction and increase after intubation were both significantly less in patients receiving bupivacaine compared with Groups L and C. Decrease after induction: $P<0.0001$; 20.3 (7.3), 28.5 (5.5) and 28.8 (7.1)% in Groups B, L, and C respectively; $P<0.001$ between Groups B and L, and between Groups B and C. Increase after intubation: $P<0.0001$; 12.4 (7.2), 26.8 (10.9), 31.8 (10.4) in Groups B, L, and C, respectively; $P<0.001$ between Groups B and L, and between Groups B and C.

There were no differences between the BIS values before and after the injection ($t_0$ and $t_1$) of local anaesthetic/saline [95.1 (1.7) at $t_0$ and 95.4 (0.8) at $t_1$, $P>0.05$]. The difference between $t_2$ and $t_3$ was also not significant [43.2 (0.8) at $t_2$ and 44.1 (2.0) at $t_3$, $P>0.05$].

At the end of the induction period, no response to verbal commands was observed (BIS <45). Awareness or inadequate analgesia was observed in no patients. Except for the hypotension in two patients in each group, haemodynamic complications were not seen. No signs of local anaesthetic toxicity or side-effects were observed in any patient.

**Discussion**

Our study showed that i.m. administration of local anaesthetics lead to a reduction in both the induction and maintenance doses of propofol to maintain the same BIS value.

The interaction of local and general anaesthetics has been investigated in several studies. Hodgson and colleagues suggested three mechanisms for the reduction of MAC of volatile anaesthetic agents when combined with epidural anaesthesia: (i) systemic general anaesthetic effects of absorbed epidural lidocaine; (ii) direct epidural sensory block of the noxious stimulus and (iii) subanaesthetic concentrations of epidural lidocaine depressing spinal cord motor function. They concluded that the MAC-sparing effect of epidural anaesthesia in combination with general anaesthesia is most likely caused by central effects of spinal deafferentation, not to the systemic effects of lidocaine nor to direct neural block of spinal nerves. Our results do not support this conclusion. In another study it has been shown that i.v. lidocaine infusion has a MAC-sparing effect of 10–28%. In our study, an i.v. anaesthetic has been used instead of inhalational anaesthetics, and lidocaine was administered via the i.m. route. It can be concluded that systemic general anaesthetic effects of absorbed local anaesthetics play an important role in the reduction of the dose of the general anaesthetic.

The effects of i.m. administration of lidocaine and bupivacaine on the induction doses of thiopental and propofol have been described. The results of these studies
and the present study are similar. However, there are two important differences. Firstly, in our study, not only the induction, but also the maintenance doses of propofol were investigated. Secondly, in these studies the effects of local anaesthetics on the general anaesthetic effect of i.v. anaesthetics were shown and compared only by the responses to verbal commands and not by BIS. In our study, both the loss of response to commands and BIS were used.

According to several studies, there are two main mechanisms that may explain the interaction of local and general anaesthetics. Firstly, most local anaesthetics bind to sodium channels in the inactivated state, preventing subsequent channel activation and the large transient sodium influx associated with membrane depolarization. General anaesthetics are known to have some effects on the central nervous system, which are not unlike those of local anaesthetics. Both volatile anaesthetics and barbiturates have been shown to block sodium channels and thus prevent action potential formation in central neurones. Immobilization of the gating charge caused by the general anaesthetics has also been implicated in local anaesthetic action. Studies show that general anaesthetics do indeed increase the proportion of channels in the closed inactive state.

Secondly, it is well known that propofol enhances GABAergic currents, which facilitate inhibitory neurotransmission in neurones. Most i.v. anaesthetics inhibit the specific GABA uptake process in vitro in striatal nerve terminals, some, such as propofol, at clinically relevant concentrations. It has been shown that local anaesthetics also potentiate GABA-mediated Cl\(^-\) currents by inhibiting GABA uptake. These common mechanisms of action of local and general anaesthetics may explain how the hypnotic effect of i.v. propofol is enhanced by i.m. administration of bupivacaine or lidocaine.

We did not observe any signs of local anaesthetic toxicity or side-effects. The highest doses of local anaesthetics administered in our study were less than half the recommended maximum clinical doses and were similar to doses administered in previous studies. Further studies are necessary to evaluate the effects of different doses of both lidocaine and bupivacaine on the doses of general anaesthetics after i.m. administration. We administered i.m. lidocaine 10 min and i.m. bupivacaine 30 min before i.v. administration of propofol because, at these times, blood concentrations reach a peak.

Changes in haemodynamic values were not the primary variable in our study. The attenuation of the cardiovascular response to intubation after i.v. lidocaine has been recognized for some time. However, there are few studies examining the effects of i.m. administration. Bupivacaine was associated with a more stable haemodynamic status after both induction and intubation compared with control and lidocaine. Similarly, both lidocaine and bupivacaine were associated with a reduced increase in heart rate after intubation. Whether these were caused by the reduction in propofol doses, or by the direct effect of the i.m.-administered local anaesthetics is unclear.

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