SCIENTIFIC ARTICLE

REMIFENTANIL VS FENTANYL DURING DAY CASE DENTAL SURGERY IN PEOPLE WITH SPECIAL NEEDS: A COMPARATIVE, PILOT STUDY OF THEIR EFFECT ON STRESS RESPONSE AND POSTOPERATIVE PAIN

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Background: People with special needs undergoing dental surgery frequently require general anesthesia. We investigated the effect of remifentanil vs fentanyl on stress response and postoperative pain in people with special needs undergoing day-case dental surgery.

Methods: Forty-six adult patients with cognitive impairment undergoing day-case dental surgery under general anesthesia were allocated to receive intraoperatively either fentanyl 50 μg iv bolus (group F, n = 23) or continuous infusion of remifentanil 0.5-1 μg/kg/min (group R, n = 23). Intraoperative hemodynamic parameters were recorded and serum inflammatory mediators [tumor necrosis factor-α, substance-P], stress hormones (melatonin, cortisol) and β-endorphin were measured. Postoperative pain was assessed during the first postoperative 12 hours with the Wong-Baker faces pain-rating scale.

Results: Demographics were similar in two groups. The two groups did not differ regarding their effects on inflammatory mediators, stress hormones and postoperative pain scores. However, the use of remifentanil prevented intraoperative increases of arterial blood pressure and heart rate.

Conclusions: Remifentanil and fentanyl did not affect differently stress and inflammatory hormones during day-case dental surgery, although remifentanil may render intraoperative management of hemodynamic responses easier. Both opioids are equally efficient for postoperative pain management following dental surgery in people with special needs.

Key words: general anesthesia, remifentanil, fentanyl, mentally disabled persons, dental surgery.

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Introduction

People with special needs (PSN) bring the anesthesiologist in front of unique challenges. Simple surgical procedures, such as day case oral surgeries, which are routinely performed under local or regional anesthesia in adult population, are frequently performed under general anesthesia in PSN\(^1\). In addition to the limited experience with general anesthesia for dental procedures, impaired communication can greatly complicate grading of pain in PSN. Internalizing mental health symptoms are common among PSN; anxiety and deteriorated kinetic function contribute to greater pain frequency and intensity, and physical fatigue in PSN\(^2,3\). Because effective relief of postoperative pain is essential for quality of health services and an earlier discharge from hospital\(^4,5\), non-verbal assessment of pain and specific assessment tools are very helpful in PSN\(^6,7\).

Simple protocols of verified efficacy can prove very helpful in managing such patients. Remifentanil is a relatively new, ultrashort-acting \(\mu\)-opioid agonist that may be useful when rapid recovery is desirable, such as in day-case dental surgery\(^8\). Due to its short half-life time, supplemental analgesia is usually needed postoperatively. On the other hand, the residual analgesic effect of fentanyl may prove advantageous. However, it is not known if this advantage applies in procedures with minor postoperative pain. In addition, the superiority of remifentanil in preventing stress response, especially during dental surgery, has not been substantiated\(^9,10,11,12,13\).

The aim of this prospective comparative study was to investigate the hypothesis whether remifentanil compared to fentanyl can induce less inflammatory and stress response to the day-case dental surgery in PSN. A secondary aim was to investigate comparatively their effect on patients’ hemodynamic response and postoperative pain.

Methods

Patients

After approval of the prospective randomized study by the Ethics Committee of “Asklepieion Voulas” General Hospital (Chairperson Dr. S.Sgouromalli-Kostaki MD, PhD, protocol number 2009/19-9-2005) and obtaining parents’ written consent, 46 patients aged 18-45 years old, ASA II were enrolled. The study was registered at Clinical Trials.doev(ID:NCT02619032) and was conducted in accordance with the Helsinki Declaration. Cognitive impairment was present in all patients in the context of autism, psychosis and neurological disorders, such as anoxic encephalopathy and epilepsy. Dental surgery was performed under general anesthesia. Dental procedures included obstruction, extraction, reconstruction of teeth and gum therapy. Some patients were subjected to more than one procedure. Exclusion criteria were: ASA>II> and expected duration of surgery >1 hour. Patients were randomly divided into Fentanyl group (group F, \(n = 23\)) and Remifentanil group (group R, \(n = 23\)) using a computer-generated randomization schedule.

Anesthetic protocol

Patients were premedicated with midazolam 1-2 mg iv and atropine 0.5 mg iv, 10 min before induction of anesthesia. Monitoring included non-invasive measurement of arterial blood pressure, electrocardiogram, pulse oxymetry, capnography and Bispectral Sedation Index (BIS\(^*\)-XR-Aspect Medical Systems\(^\text{TM}\). Intl., B.V., Leiden, Netherlands). Monitoring was recorded continuously and data was collected at 15 min intervals until surgery was completed (end-point was defined as the last dental-surgical manipulation). Maintenance of circulating volume was achieved with Ringer’s Lactate solution at 3 ml/kg/h infusion rate.

In group F, anesthesia was induced with propofol 3 mg/kg iv and one single dose of fentanyl 50 \(\mu\)g iv. Nasal tracheal intubation was facilitated with administration of succinylcholine 1.5 mg/kg iv. No analgesics for postoperative pain were given thereafter.

In group R, anesthesia was induced with an initial infusion rate of remifentanil 0.5-1 \(\mu\)g/kg/min for 5 min (using a 50 mcg/ml remifentanil solution) and co-administration of a bolus dose of propofol 1.5 mg/kg. Nasal tracheal intubation was facilitated with administration of succinylcholine 1.5 mg/kg iv. Afterwards, remifentanil infusion was instituted at
0.25 μg/kg/min and the rate of infusion was titrated to maintain heart rate and systolic blood pressure ± 20% of baseline values. Remifentanil infusion was interrupted upon completion of surgical intervention. No analgesics for postoperative pain were given before remifentanil infusion was stopped.

In both groups, neuromuscular blockade was achieved by rocuronium 0.6 mg/kg iv and repetitive doses of rocuronium of 10 mg iv, if needed. The maintenance of anaesthesia was performed by repetitive doses of propofol 15-20 mg iv, in order to maintain BIS-values between 40-50. The lungs were ventilated with a mixture of 40% oxygen in air, tidal volume of 8 ml/kg and breath rate titrated to maintain end-tidal CO₂ 35-40 mmHg. Intraoperatively, patients in both groups received granisetron (Kytril® Roche Labs., London, UK) 3 mg, methylprednisolone (Solu-medrol® Pfizer, Hellas) 125 mg and clindamycin (Dalacin-C, Pfizer, Hellas) 600 mg iv. Atropine 0.02 mg/kg and neostigmine (0.05 mg/kg) were administered to all patients to reverse neuromuscular block and facilitate tracheal extubation.

Patients remained under surveillance in the post-anesthesia care unit [PACU] for 3 h. Postoperative pain was assessed for the first 12 postoperative hours, at 30 min time-intervals for the first 3 hours, and every 3 hours thereafter by an independent observer, blinded to the study group, using the Wong-Baker faces pain rating scale (0-6). If pain scores were ≥3 a rescue dose of paracetamol 12.5 mg/kg iv was administered. The time of first dose given and the total paracetamol doses given during the observation period of the study were recorded.

Samples

Inflammation markers, along with stress hormones (cortisol, TNF-a, substance-P, melatonin and β-endorphin) were measured in each patient at three different time-points: T1: blood sample collection upon intravenous catheter insertion (baseline value), T2: after tracheal intubation and T3: at the end of operation (after surgical manipulation completion).

Outcomes

The primary end-points of our study were the values of inflammation markers and stress hormones for all time-points examined. Secondary outcomes were postoperative pain scores and paracetamol rescue doses given, as well as intraoperative hemodynamic response including variations of arterial pressure and heart rate.

Statistical analysis

Data are expressed as Mean ± Standard Deviation for continuous variables and as percentages for categorical data. The Kolmogorov-Smirnov test was used to assess the normality of the distributions. Continuous variables were compared using Student’s unpaired t-test. Comparisons of continuous normally distributed related variables were performed utilizing Repeated Measures ANOVA with Holm’s post-hoc analysis. All performed tests were two-sided. A p value less than 0.05 was considered statistically significant. Statistical Analysis was performed using SPSS 17.0 (Windows Version).

Results

All participants completed the study protocol; 23 participants in each group, respectively. The two groups did not differ regarding their demographic characteristics, except age and weight which is not of clinical significance. Demographic characteristics and pre-existing pathology of the patients are presented in Tables 1 and 2, respectively.

No statistically significant differences were
**Table 2**

<table>
<thead>
<tr>
<th>Neurological disorder</th>
<th>Group R (n = 23)</th>
<th>Percentage</th>
<th>Group F (n = 23)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental retardation</td>
<td>8</td>
<td>34.78%</td>
<td>14</td>
<td>60.87%</td>
</tr>
<tr>
<td>Autism</td>
<td>8</td>
<td>34.78%</td>
<td>6</td>
<td>26.09%</td>
</tr>
<tr>
<td>Anoxemic Encephalopathy</td>
<td>-</td>
<td>0%</td>
<td>1</td>
<td>4.35%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>2</td>
<td>8.69%</td>
<td>1</td>
<td>4.35%</td>
</tr>
<tr>
<td>Down Syndrome</td>
<td>2</td>
<td>8.69%</td>
<td>1</td>
<td>4.35%</td>
</tr>
<tr>
<td>Kruzon Syndrome</td>
<td>1</td>
<td>4.35%</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>Dandy Walker Syndrome</td>
<td>1</td>
<td>4.35%</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>Trauma</td>
<td>1</td>
<td>4.35%</td>
<td>-</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Table 3**

Inflammatory mediators and stress hormones during surgery in two groups. Data is presented as mean± standard deviation

<table>
<thead>
<tr>
<th>Cortisol (mg/dl)</th>
<th>Group F (n = 23)</th>
<th>Group R (n = 23)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline value</td>
<td>16.66 ± 5.83</td>
<td>19.00 ± 8.84</td>
<td>0.29</td>
</tr>
<tr>
<td>Immediately after intubation</td>
<td>25.12 ± 10.87</td>
<td>27.48 ± 9.29</td>
<td>0.43</td>
</tr>
<tr>
<td>At the end of operation</td>
<td>19.40 ± 9.31</td>
<td>18.89 ± 8.86</td>
<td>0.85</td>
</tr>
</tbody>
</table>

| β-Endorphin (ng/ml)           |                  |                  |     |
| Baseline value                | 1.00 ± 0.62      | 1.61 ± 1.74      | 0.49|
| Immediately after intubation  | 1.05 ± 0.78      | 1.25 ± 0.93      | 0.47|
| At the end of operation       | 0.91 ± 0.58      | 1.80 ± 2.18      | 0.1 |

| TNF-a (pg/ml)                 |                  |                  |     |
| Baseline value                | 5.77 ± 1.95      | 5.73 ± 2.18      | 0.38|
| Immediately after intubation  | 5.91 ± 2.10      | 5.96 ± 1.49      | 0.92|
| At the end of operation       | 6.27 ± 1.67      | 6.10 ± 1.50      | 0.74|

| Substance-P (ng/ml)           |                  |                  |     |
| Baseline value                | 0.41 ± 0.22      | 0.39 ± 0.28      | 0.76|
| Immediately after intubation  | 0.41 ± 0.22      | 0.41 ± 0.28      | 0.95|
| At the end of operation       | 0.39 ± 0.23      | 0.35 ± 0.28      | 0.66|

| Melatonin (pg/ml)             |                  |                  |     |
| Baseline value                | 6.33 ± 13.36     | 3.90 ± 4.87      | 0.51|
| Immediately after intubation  | 6.26 ± 14.36     | 2.10 ± 3.19      | 0.97|
| At the end of operation       | 5.65 ± 9.67      | 1.78 ± 2.29      | 0.59|

**Fig. 1**

A time-value graph of mean values of pain rating scores on Wong-Baker faces pain rating scale in postoperative period in the two groups.
Remifentanil vs fentanyl for dental surgeries

detected regarding inflammatory mediators and stress hormones during surgery between the two groups at all examined time intervals (Table 3).

Regarding post-operative pain no statistically significant differences were observed between the two groups during the first 12 post-operative hours, though the group R exhibited higher mean pain scores during the first 6 hours (Fig. 1). However, no patient required paracetamol as rescue dose, in both groups.

Significant differences were observed in hemodynamic parameters between the two groups. The remifentanil group exhibited significantly lower values of systolic and diastolic blood pressure at all time intervals (Figs. 2 and 3, respectively), as well as significantly lower heart rate immediately after intubation and 60 min afterwards (Fig. 4).

Discussion

The present study did not show any differences between the two groups regarding the inflammatory and stress response, though a significant difference was observed regarding the intraoperative hemodynamic response. Similarly to our results, several other studies have shown that dental surgery leads to an intraoperative hemodynamic response. In our study, the titration of the continuous infusion of remifentanil achieved better control of the hemodynamic parameters comparing to the bolus dose of fentanyl. The above effect was due to its unique kinetic profile that allows its continuous infusion and facilitates its titration according to continuously changing intensity of surgical stimuli. We investigated the hypothesis that this fact could have suppressed stress response at different time points. However, despite the different administration scheme of the two drugs and the favorable effect of remifentanil on hemodynamics, stress response was not altered by remifentanil.

Since baseline values of stress hormones in our study are within normal range and no statistical change was observed during the procedure, it seems that dental surgery does not affect stress response, which is in contradiction with other studies. In the present study, regarding inflammatory response, no differences were observed in levels of β-endorphin between the two
groups. The same applied for TNF-α, substance-P and melatonin. Remifentanil has been found to suppress TNF-α in two experimental studies\textsuperscript{9,10} both in humans and rats, but it seems to have no effect on cortisol levels when co-administered with propofol\textsuperscript{12,13,17}. Besides, the intraoperative administration of methyl-prednizolone given in our study would probably suppress the stress response in such a procedure. According to our knowledge, comparative studies of remifentanil and fentanyl in terms of other inflammatory mediators and endogenous opioids are not available for minor procedures.

Regarding our secondary goal, the present study did not reveal any difference between the two groups concerning the postoperative pain intensity. It should be emphasized that the pain scale used in this study has been previously validated\textsuperscript{18}. It is also noteworthy that the low pain scores in both groups minimized the need for adjunct analgesic drug acting on post-operative period. Of interest, although it is expected for the remifentanil group to experience some pain (due to absence of intraoperative analgesic co-treatment) at least at the immediate post-operative period, none of the participants seemed to do so. Probably, two factors might contribute to this observation: the mild degree of pain experienced and the analgesic effects of propofol and methylprednizolone. This is in support of previous data showing that propofol is likely to have antinociceptive action\textsuperscript{19} and that corticosteroids reduce pain and opioid consumption after orthopedic and dental surgery\textsuperscript{20,21}. Therefore, it appears that both analgesic protocols are equally effective for relieving post-operative pain after dental procedures, practically abolishing the need of additional administration of analgesics in day-case dental procedures in PSN.

**Limitations**

The relatively small number of participants and the diversity of underlying dental and neurological disease could limit our conclusions. Any presence of inflammation or anomalies in autonomic function, particularly of central origin, could have had an effect on stress response and inflammatory mediators, thereby eliminating any differences between the study groups. A more careful future classification of the kind of dental surgery performed and pre-existing dental disease might help detect any slight differences.

**Summary**

Although remifentanil prevented more efficiently the intraoperative hemodynamic response to surgical stimuli, this did not result in differences in circulating stress and inflammatory hormones compared to fentanyl. Thus, remifentanil and fentanyl may be considered equivalent in terms of surgical stress for PSN during day case dental surgery. Importantly, in this type of surgery, equivalent success in postoperative pain management can be expected with both opioids.

**Acknowledgments**

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References


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- 98% of BRIDION patients recovered to a TOF* ratio of 0.9 from reappearance of T2 † within 5 minutes‡
- 97% of BRIDION patients recovered to a TOF* ratio of 0.9 from 1 to 2 PTCs † within 5 minutes§

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Volunteer studies have demonstrated a slight (13%-22%) and transient (<30 minutes) prolongation of the prothrombin time/activated partial thromboplastin time (PT/aPTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on peri- or postoperative bleeding complications with BRIDION alone or in combination with anticoagulants. As BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants, caution should be exercised in patients on anticoagulation for a pre-existing or coronary condition. This pharmacodynamic interaction is not clinically relevant for patients receiving routine postoperative prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exceptions of toremifene, fusidic acid, and hormonal contraceptives.

REFERENCES:
1. BRIDION Summary of Product Characteristics (SPC).

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