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“For some must watch, while some must sleep” (Hamlet-Act. III, Sc. ii).

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“For some must watch, while some must sleep”

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The neuromuscular blockade is required within 24 hours of BRIDION administration, a normalised neuromuscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dysgeusia (metal or bitter taste) and asthenic reactions (movement, coughing, straining, or sucking on the endotracheal tube). In patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION was uncertain. In a few individuals, allergic-like reactions (e.g., flushing, erythematous rash) following BRIDION were reported. Patients should be prepared for the possibility of allergic reactions and take the necessary precautions. It is a clinical practice to shorten the intervention time for the premedication time (PPR) or the intervention time (PPR) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on perioperative 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 with anticoagulants or a prothrombin time or an activated partial thromboplastin time (APTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on perioperative 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 with anticoagulants or a prothrombin time or an activated partial thromboplastin time (APTT) with BRIDION; however, clinical studies have demonstrated no clinically relevant effect on perioperative bleeding complications with BRIDION alone or in combination with anticoagulants.

**REFERENCES**

1. BRIDION Summary of Product Characteristics (SPC).

Please see summary of product characteristics for full prescribing information.

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PALPATE INTERCISTAL LINE CORRECTLY: NOT TRANSGRESS TOO HIGH: CAN BE TOO CLOSE TO CONUS MEDULLARIS"

Deepak Gupta 595
Neostigmine is the classic acetylcholinesterase antagonist, which is widely used for reversal of neuromuscular block of all nondepolarising relaxants. This is a pharmacodynamic effect secondary to inhibition of the acetylcholine esterase at the neuromuscular endplate, resulting in a subsequent increased and prolonged effect of acetylcholine on the free endplate receptors. That is why, an overdose of nondepolarising muscle relaxant, blocking the entire endplate receptors’ pool cannot be antagonized by neostigmine resulting in the so-called “neostigmine-resistant curarization”.

“Neostigmine-resistant curarization” has been described by Hunter 1956. However, Churchill-Davidson (1959) stressed the fact that there are many causes of prolonged cessation of respiration, and before the term “neostigmine-resistant-curarization” can be accepted, it is first necessary to prove that a neuromuscular block is in fact present, and secondly that neostigmine fails to reverse the block.

Using the isolated phrenic nerve diaphragm preparation, immersed in Krebs solution. Baraka (1964) demonstrated that there is a ceiling to the maximum reversal capacity of neostigmine. Neostigmine could not reverse neuromuscular block of an overdose of tubocurarine which was added to the perfusion bath. This in-vitro observation was confirmed in vivo by Baraka (1967) who showed in man that reversal of neuromuscular block by neostigmine depended on the degree of neuromuscular block and the plasma level of tubocurarine at the time of reversal. Neostigmine could not reverse the doses of tubocurarine that are much greater than the blocking dose. In addition, the report showed that the plasma level of tubocurarine following reversal by neostigmine is not significantly different from that observed without neostigmine reversal, suggesting the fact that reversal of nondepolarising block by neostigmine is a pharmacodynamic, and not a pharmacokinetic effect. This finding has been confirmed by Waser who showed that the radioactive curare concentration in the diaphragm remains the same before and after reversal of neuromuscular block by neostigmine. That is why, reversal of curare by neostigmine cannot be achieved if the whole endplate receptor pool is occupied by the neuromuscular blocker.

The degree of reversal of nondepolarising neuromuscular block by neostigmine can be monitored by the train-of-four fade (Hassan Ali et al, 1975). T-O-F fade ratio <0.7-0.9 is associated with upper airway obstruction, inadequate recovery of pulmonary function, reduced pharyngeal muscle coordination, increased risk of aspiration, and impaired hypoxic ventilation response.

Because of the possible limitations, and muscarinic side-effects of the pharmacodynamic reversal of neuromuscular block by neostigmine, the possibility of pharmacokinetic reversal by
Sugammadex (a modified gamma cyclodextrin) has been recently introduced into clinical anesthesiology practice. As mentioned by Miller, and Naguib, the introduction of sugammadex is another milestone in clinical neuromuscular pharmacology, which provides an opportunity to change the practice of anesthesiology.

Sugammadex offers a new approach for reversal of nondepolarising neuromuscular block; it exerts its reversal effect by forming very tight combination in a 1:1 ratio with the steroidal neuromuscular blocking agents (rocuronium > vecuronium > pancuronium) (Bom et al 2002). Intravenous administration of sugammadex during rocuronium-induced neuromuscular blockade results in a guest-host complex in equilibrium with a very high association rate and very low dissociation rate resulting in rapid removal of free rocuronium from the plasma. This creates a concentration gradient favoring movement of rocuronium from the neuromuscular junction into plasma where it is encapsulated by the free sugammadex molecules. Therefore, the neuromuscular blockade of rocuronium is terminated rapidly by the diffusion of rocuronium away from the neuromuscular junction into the plasma.

In the absence of sugammadex, rocuronium is eliminated mainly by biliary excretion (>75%), and to a lesser extent degree by renal excretion (10%-25%). However, because of the soluble nature of the rocuronium-cyclodextrin complex, urinary excretion becomes the major route of elimination. One of the features that makes sugammadex so different from anticholinesterases is that it takes effect more quickly and reliably than neostigmine, even when an overdose of the nondepolarising relaxants is occupying the entire endplate receptor pool.

In conclusion, reversal of nondepolarising neuromuscular block by neostigmine is a pharmacodynamic effect secondary to inhibition of the acetylcholine-esterase. The accumulated acetylcholine will act on the free endplate receptors. Thus, an overdose of nondepolarising relaxants blocking the whole receptors’ pool cannot be reversed by neostigmine resulting in the so-called “Neostigmine-resistant curarization”. The advantage of reversal of nondepolarising block by neostigmine is its low cost, and its broad spectrum reversal of all nondepolarising relaxants.

The advantage of sugammadex for reversal of nondepolarising neuromuscular block is the absence of the muscarinic side-effects of neostigmine. Also, it can reverse the neuromuscular, even in the presence of an overdose blocking the whole receptors’ pool. However, the reversal effect of sugammadex is limited to the steroidal neuromuscular blockers such as rocuronium. Also, its cost is much higher than that of neostigmine.

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American University of Beirut
Beirut - LEBANON

References

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). Intraperative 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.
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. 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. Because effective relief of postoperative pain is essential for quality of health services and an earlier discharge from hospital, non-verbal assessment of pain and specific assessment tools are very helpful in PSN.

Simple protocols of verified efficacy can prove very helpful in managing such patients. Remifentanil is a relatively new, ultrashort-acting μ-opioid agonist that may be useful when rapid recovery is desirable, such as in day-case dental surgery. 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.

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.gov (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™, 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 μg 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 μg/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
Underlying neurological disorders in two groups

<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>
<tr>
<td>β-Endorphin (ng/ml)</td>
<td>1.00 ± 0.62</td>
<td>1.61 ± 1.74</td>
<td>0.49</td>
</tr>
<tr>
<td>Baseline value</td>
<td>1.05 ± 0.78</td>
<td>1.25 ± 0.93</td>
<td>0.47</td>
</tr>
<tr>
<td>Immediately after intubation</td>
<td>0.91 ± 0.58</td>
<td>1.80 ± 2.18</td>
<td>0.1</td>
</tr>
<tr>
<td>At the end of operation</td>
<td>0.91 ± 0.58</td>
<td>1.80 ± 2.18</td>
<td>0.1</td>
</tr>
<tr>
<td>TNF-a (pg/ml)</td>
<td>5.77 ± 1.95</td>
<td>5.73 ± 2.18</td>
<td>0.38</td>
</tr>
<tr>
<td>Baseline value</td>
<td>5.91 ± 2.10</td>
<td>5.96 ± 1.49</td>
<td>0.92</td>
</tr>
<tr>
<td>Immediately after intubation</td>
<td>6.27 ± 1.67</td>
<td>6.10 ± 1.50</td>
<td>0.74</td>
</tr>
<tr>
<td>At the end of operation</td>
<td>6.27 ± 1.67</td>
<td>6.10 ± 1.50</td>
<td>0.74</td>
</tr>
<tr>
<td>Substance-P (ng/ml)</td>
<td>0.41 ± 0.22</td>
<td>0.39 ± 0.28</td>
<td>0.76</td>
</tr>
<tr>
<td>Baseline value</td>
<td>0.41 ± 0.22</td>
<td>0.41 ± 0.28</td>
<td>0.95</td>
</tr>
<tr>
<td>Immediately after intubation</td>
<td>0.39 ± 0.23</td>
<td>0.35 ± 0.28</td>
<td>0.66</td>
</tr>
<tr>
<td>At the end of operation</td>
<td>0.39 ± 0.23</td>
<td>0.35 ± 0.28</td>
<td>0.66</td>
</tr>
<tr>
<td>Melatonin (pg/ml)</td>
<td>6.33 ± 13.36</td>
<td>3.90 ± 4.87</td>
<td>0.51</td>
</tr>
<tr>
<td>Baseline value</td>
<td>6.26 ± 14.36</td>
<td>2.10 ± 3.19</td>
<td>0.97</td>
</tr>
<tr>
<td>Immediately after intubation</td>
<td>5.65 ± 9.67</td>
<td>1.78 ± 2.29</td>
<td>0.59</td>
</tr>
<tr>
<td>At the end of operation</td>
<td>5.65 ± 9.67</td>
<td>1.78 ± 2.29</td>
<td>0.59</td>
</tr>
</tbody>
</table>

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
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.
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.

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COMPARISON OF THE BONFILS INTUBATION FIBRESCOPE VERSUS C-MAC VIDEOLARYNGOSCOPE

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Background: This prospective, randomized, single blind, single operator study was conducted to compare hemodynamic responses when endotracheal intubation was performed using the Bonfils intubation fibrescope versus the C-MAC videolaryngoscope.

Method: Forty-four ASA I patients aged between 18 and 60 years, scheduled for elective surgery requiring endotracheal intubation were recruited. They were randomized into the Bonfils group or C-MAC group. Hemodynamic changes, laryngeal view, duration of intubation and post intubation complications were evaluated. Mean arterial pressure, heart rate and oxygen saturation were monitored pre and post-induction, pre and post-intubation, and at 1 minute intervals thereafter for 10 minutes.

Results: Endotracheal intubation was successful at first attempt in 90.9% in both groups. Heart rate was significantly higher in the Bonfils group \( (p<0.05) \) compared to the C-MAC group and values were sustained throughout the study. There was no difference in the mean arterial pressure (MAP) between the two groups. Mean time to intubation was significantly longer in the Bonfils group (28.8 vs. 24.7 seconds, \( p = 0.02 \)). There were no significant differences in laryngeal view and post intubation complications between the groups.

Conclusion: Intubation using the Bonfils intubation fibrescope took longer, and resulted in significantly higher heart rate when compared with the C-MAC videolaryngoscope.

Introduction

Securing the airway with a cuffed endotracheal tube provides protection against aspiration and allows application of controlled mechanical ventilation. The Macintosh laryngoscope described in 1943 is most commonly used and remains the gold standard device for endotracheal intubation. Direct laryngoscopy and tracheal intubation causes marked stress responses, increasing heart rate and blood pressure due to direct stimulation at the tongue base and placement of endotracheal tube through the vocal cords\(^1\,^2\). These transient sympathetically-driven responses produce adverse respiratory and cardiovascular complications which may be hazardous in patients with pre-existing hypertension and severe cardiac diseases\(^3\).

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In recent years, video assisted laryngoscopes such as the Glidescope (Verathon, Bothell, Washington, USA), Pentax Airway Scope (Pentax, Tokyo, Japan), Airtraq (Prodol Meditec S.A., Vizcaya, Spain) and C-MAC (Karl Storz Endoscope Ltd, Tuttlingen, Germany) have been developed to improve laryngeal view, hence obviate the need for excessive manipulation which might provoke increased sympathetic responses. Video laryngoscopy has also increased the rate of successful endotracheal intubation in patients with difficult airway. Other new intubation tools include the intubating laryngeal mask airway, lightwand intubating device (Trachlight), styletscope (NihonKohden, Tokyo, Japan), fibreoptic bronchoscope and the Bonfils intubation fibrescope (Karl Storz Endoscope Ltd, Tuttlingen, Germany) which all facilitate endotracheal intubation without direct laryngoscopy.

The C-MAC (Karl Storz Endoscope Ltd, Tuttlingen, Germany) videolaryngoscope is a modification of the Storz Berci-Kaplan DCI. It consists of a Macintosh Blade with a light source and an integrated video camera connected via a cable to a video display monitor onto which the image at the blade camera is projected. Studies have shown that indirect laryngoscopy with the C-MAC videolaryngoscope improved laryngeal view and caused less hemodynamic stress response compared to direct laryngoscopy.

The Bonfils intubation fibrescope (Karl Storz Endoscope Ltd, Tuttlingen, Germany) described by Bonfils in 1983, is a 40 cm long, thin rigid fibreoptic endoscope used for endotracheal intubation. This video assisted intubation fibrescope allows visualization of the laryngeal inlet and placement of the endotracheal tube under direct vision. Theoretically, avoidance of direct laryngoscopy would cause less oropharyngeal stimulation thus attenuating the hemodynamic stress response. Najafi et al found that the Bonfils intubation fibrescope compared well with the Macintosh laryngoscope in terms of intubation conditions and success rate, with less mechanical stress and hemodynamic disturbance.

Methods

This was a prospective, randomized, single blind study, which was conducted in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) between November 2014 and April 2015, following approval from the Medical Research and Ethics Committee UKMMC.

Forty-four patients aged between 18-60 years, of body mass index (BMI) <35 kg/m², physical status of American Society of Anesthesiologists (ASA) class I, without anticipated difficult airway, scheduled for elective surgery under general anesthesia requiring endotracheal intubation were recruited. Patients were briefed on the study and written informed consent was obtained. Each patient was assigned by a computer-generated randomization to either the Bonfils group or C-MAC group. Endotracheal intubation using both devices was performed by a single operator, who was a postgraduate anesthesiology trainee with experience of more than 20 successful intubations each with the Bonfils intubation fibrescope and C-MAC videolaryngoscope, prior to commencement of the study.

All patients were fasted for at least 6 hours, and received oral midazolam 3.75 mg or 7.5 mg the night and morning before surgery. In the operating theatre, the patient was randomly assigned to either the Bonfils group or C-MAC group. Cuffed Portex endotracheal tubes with internal diameters of 7.0 or 7.5 mm were used for the female patients and 7.5 or 8.0 mm for the male patients.

Before induction of anesthesia, the patient was positioned supine with the head rested on a silicon head rest, in optimal intubation position. Standard monitoring comprising non-invasive blood pressure (NIBP), electrocardiography (ECG) and pulse oximetry was instituted, and the patient was commenced on maintenance infusion of Ringer’s lactate solution. Baseline mean (MAP), systolic (SBP) and diastolic (DBP) blood pressures, heart rate (HR) and oxygen
saturation (SpO$_2$) were recorded.

After 3 minutes of pre-oxygenation, anesthesia was induced with IV fentanyl 2 mcg/kg and propofol 2 mg/kg till loss of eyelash reflex, followed by paralysis with rocuronium 0.6 mg/kg. The patient was then manually ventilated via facemask with sevoflurane in 100% oxygen, targeted to a minimum alveolar concentration (MAC) of 1.0 to 1.2. Three minutes after administration of rocuronium, endotracheal intubation was performed using either the Bonfils intubation fibrescope or C-MAC videolaryngoscope. The endotracheal tube cuff was inflated and correct tube placement confirmed by the presence of end tidal carbon dioxide (ETCO$_2$) via capnography. The patients were subsequently connected to the ventilator and put on volume control mode with ETCO$_2$ ranging 35 to 40 mmHg. Anesthesia was maintained with sevoflurane, titrated to a MAC of 1.0 to 1.2, in a mixture of air and oxygen at a ratio of 1:1, with gas flows at 1 L/min. Mean arterial pressure, SBP, DBP, HR and SpO$_2$ were recorded by an observer before and after induction of anesthesia, before and immediately after intubation, and every 1 minute thereafter for the subsequent 10 minutes. Hemodynamic parameters were documented before induction of anesthesia as time A, after induction as time B, prior to intubation as time C, and after intubation as time D.

In the Bonfils group, endotracheal intubation was performed using the Bonfils intubation fibrescope via midline approach$^{13}$. The endotracheal tube was loaded on and taped to the proximal end of the lubricated shaft of the Bonfils intubation fibrescope. After adjusting the fibrescope to optimal view on the display monitor, anti-fog solution was applied to its distal tip. The operating bed was adjusted to allow the operator optimal manipulation of the Bonfils intubation fibrescope. The assisting anesthetic doctor performed a gentle jaw thrust maneuver, or the operator performed the tongue jaw lift on the patient to lift the tongue from obstructing subsequent viewing with the fibrescope. The fibrescope was held in the operator’s dominant hand and introduced midline into the patient’s oral cavity, angled end of the scope faced anteriorly and the length of the fibrescope at 60 degree angle to the patient’s body. Upon visualization of the uvula, the fibrescope was tilted gradually towards the operator while advancing it down the oropharynx towards the epiglottis. The fibrescope was further advanced posterior to the epiglottis and the laryngeal inlet sought. The view of the retropharyngeal space was improved by careful re-adjustment of the jaw thrust or tongue jaw lift maneuver. If the tongue or epiglottis persistently obstructed laryngeal view, intubation was re-attempted with a Macintosh laryngoscope in the left hand, used to laterally displace the tongue, with or without the jaw thrust$^{14}$. The rigid fibrescope was advanced just past the vocal cords and the endotracheal tube railroaded into the trachea by the assistant allowing intubation under direct vision.

In the C-MAC group, endotracheal intubation was done using the C-MAC videolaryngoscope with blades size 3 or 4. Backward and upward pressure on the cricoid cartilage was applied by the assisting anesthetic doctor as necessary, to improve laryngeal view.

The duration before successful intubation or time to intubation (TTI) was recorded by an observer, commencing from insertion of the intubating device into the patient’s mouth until confirmation of endotracheal tube placement. The number of intubation attempts was defined as the number of insertions of the intubation device into the patient’s oral cavity. Cormack and Lehane grades of I to IV was recorded based on the observed laryngeal view on the monitor, on the first attempt at endotracheal intubation.

In the event of unsuccessful intubation, the patient was manually ventilated via facemask in between intubation attempts with sevoflurane in 100% oxygen. The operator was allowed to use the same intubation device during the second intubation attempt with modification in technique of intubation such as readjustment of jaw thrust in the Bonfils group, and application of external laryngeal pressure, repositioning of the patient’s head, varying the lifting force on the laryngoscope or use of airway adjuncts such as the gum elastic bougie in the C-MAC group. The number of intubation attempts and techniques of manipulation were recorded by an observer. Subsequent analysis was based on data pertaining to successful intubation at first attempt.

Failed intubation was defined as intubation requiring more than 180 seconds or more than 2
attempts, or resulting in reduction in SpO₂ to less than 95% or esophageal intubation. These patients were subsequently intubated with the conventional laryngoscope and managed accordingly as guided by the American Society of Anesthesiologists Difficult Airway Algorithm\(^1\). Complications such as SpO₂ less than 95%, soft tissue trauma or post-operative sore throat were documented. The observer who was in charge of all data collection was not blinded to the intubation device used.

**Statistical Analysis**

Sample size was calculated using the G power sample size calculator 3.1.7 based on Najafi *et al*’s study\(^6\). Forty-four subjects were required for this study taking into consideration a 20% drop-out rate. The power of the study was taken at 0.8 with a Type I error of 0.05.

Chi-square test was used to analyze categorical data such as race and gender, Cormack and Lehane grade and post-intubation complications. The independent t-test was used to determine significant differences in hemodynamic data and continuous variables such as age, weight, height, BMI and intubation time between the two groups. Paired-sample t-test was used to compare the hemodynamic changes between baseline and post-intubation time within the groups. For non-parametric data, the Wilcoxon Signed-Rank test was used to examine the variables. A p-value <0.05 was considered statistically significant.

**Results**

Forty-four patients were recruited with equal numbers in each group. Endotracheal intubation at first attempt was successful in 20 out of 22 patients (90.9%) in both the Bonfils and C-MAC group. Four patients required a second intubation attempt where they were successfully intubated with the same initial intubation device and by the same operator. Hence, 40 patients were subsequently analyzed. Demographic data are shown in Table 1. There was no significant difference between the groups with regards to age, weight, height, BMI, gender and race.

Intubation related data are shown in Table 2. The mean TTI was significantly longer in the Bonfils group compared with the C-MAC group, \(p = 0.02\). All patients in both groups who were successfully intubated at first attempt had a Grade I Cormack and Lehane view. None of the patients required rescue intubation by the specialist or consultant in charge. No patient had oxygen saturation (SpO₂) less than 95%. Patients in both groups sustained postoperative soft tissue trauma and sore throat, but the difference was not significant.
Fig. 1 shows comparable baseline mean MAP between the groups. Mean MAP was significantly higher in the Bonfils group at 2 minutes post intubation (87.4 ± 15.0 vs 80.4 ± 10.3 mmHg, \( p < 0.05 \)), however the values in both groups were below baseline.

Table 3 shows significant reduction of mean MAP in both groups, from values before induction of anesthesia compared to values after induction and prior to intubation. Following intubation, mean MAP was significantly lower from baseline values, from 2 to 10 minutes in the Bonfils group, and from 1 to 10 minutes in the C-MAC group.

Fig. 2 shows comparable baseline mean HR between the groups. Mean HR was significantly higher in the Bonfils group at 2 (94.3 ± 14.3 vs 84.6 ± 16.4), 3 (91.6 ± 12.7 vs 82.5 ± 17.8), 5 (88.5 ± 12.5 vs 79.0 ± 17.0), 6 (87.8 ± 14.1 vs 78.6 ± 18.5), 9 (84.8 ± 13.2 vs 76.6 ± 16.8) and 10 (84.6 ± 13.9 vs 74.8 ± 17.2) minutes post intubation.

Table 4 shows significant increase in mean HR from baseline values in both groups immediately after intubation. In the C-MAC group, mean HR was not significantly different from baseline values from 1 to 9 minutes after intubation. However in the Bonfils group, mean HR was significantly higher than baseline after intubation, and in subsequent measured time intervals thereafter.
Fig. 1
Mean MAP between Bonfils and CMAC groups

Fig. 2
Mean heart rate between Bonfils and CMAC groups
Discussion

The Bonfils intubation fibrescope and C-MAC videolaryngoscope are video assisted indirect laryngoscopic devices which have been shown to improve laryngeal view while inducing minimal stress responses. The C-MAC videolaryngoscope, with its simplicity of use, has gained widespread popularity in contrast to the Bonfils intubation fibrescope which is not widely used in routine clinical practice. However the Bonfils intubation fibrescope has its advantage over the C-MAC videolaryngoscope in difficult airway situations where restricted mouth opening may limit use of the latter.

Several studies have reported desirable hemodynamic parameters with use of the Bonfils intubation fibrescope. Boker et al found that increase in MAP and HR was greater during laryngoscopy with the conventional laryngoscope than with the Bonfils intubation fibrescope. Najafi et al also found better hemodynamic profile with the latter and comparable intubation conditions even without neuromuscular blockade. To date, there has been no study comparing hemodynamic changes during intubation with the Bonfils intubation fibrescope compared to the C-MAC videolaryngoscope. We found significant increase in HR although the MAP remained comparable following intubation with the Bonfils intubation fibrescope compared to the C-MAC videolaryngoscope.

The sustained sympathetic response throughout our study was only seen with regards to the relative tachycardia following intubation with the Bonfils intubation fibrescope. Mean arterial pressures decreased below baseline values and this could be due to the vasodilatory effects of the anesthetic induction agents. King et al found that laryngoscopy and intubation during deep anesthesia obtunded any anticipated increase in MAP but reflex tachycardia was intense and persistent. The persistently high HR in the Bonfils group could also be due to the jaw thrust or tongue jaw lift maneuver. Neither of these maneuvers was applied in our patients in the C-MAC group. Park et al found that the jaw thrust increased MAP and HR irrespective of the magnitude of thrust force applied. Our patients in the C-MAC group had transient increase in HR immediately following laryngoscopy and intubation which was most likely due to oropharyngeal stimulation during laryngoscopy. McCoy et al reported that minimal force and movement during laryngoscopy could lead to the absence of the stress response. This was possible when using the C-MAC videolaryngoscope which has been known to produce better Cormack and Lehane view without the need for excessive manipulation, thus enabling higher rates of successful endotracheal intubation in predicted difficult airways.

Stoelting et al found it necessary to attenuate pressor responses using topical or IV lignocaine during laryngoscopy and intubation which exceeded 30 seconds. This may explain the hemodynamic changes in the Bonfils group as the TTI in our study was longer with a mean of 28.8 ± 6.6 seconds, compared to the C-MAC group with mean TTI of 24.7 ± 5 seconds, p=0.02. Although the longer TTI in the Bonfils group produced a significantly increased heart rate, clinically we found that heart rate did not exceed 110 beats per minute with the highest documented increase of 22% above baseline. There was also no clinically associated cardiorespiratory compromise recorded. However our patients were of ASA I physical status, thus precautionary measures to attenuate undesirable pressor responses in susceptible patients may be necessary. Despite the longer TTI with the Bonfils intubation fibrescope, the use of either device had similar rates of successful intubation at the first attempt, and post-intubation complications. There were no serious complications, and oxygenation was well maintained throughout the study in both groups.

Our TTI compared well with Halligan et al and Najafi et al who recorded median TTI of 33 seconds and 40 seconds respectively, using the Bonfils intubation fibrescope. Boker et al on the other hand, demonstrated good hemodynamic profiles with successful Bonfils retromolar intubation at a mean TTI of 14 seconds11.

The C-MAC group had a shorter TTI as it was easier to use due to familiarity with the device which was physically similar to the conventional direct laryngoscope. However, not all patients had optimal laryngeal views when intubated with the C-MAC videolaryngoscope. In our study, two patients required two intubation attempts due to unanticipated difficult
These patients had Cormack and Lehane grades II and III and were successfully intubated using the C-MAC videolaryngoscope, and a gum elastic bougie with cricoid pressure applied. Ng et al found that the C-MAC videolaryngoscope produced good laryngeal views which did not always guarantee ease and success in endotracheal tube insertion. Two patients in the Bonfils group required more than one intubation attempt due to pooling of oropharyngeal secretion that was obstructing the laryngeal view. Oropharyngeal secretion blocked the distal viewing port and absence of a suction channel hindered further advancement of the Bonfils intubation fibrescope as airway structures were obscured. Halligan et al found that postural adjustment and intubation with the aid of the direct conventional laryngoscope was rarely required in patients planned for intubation with the Bonfils intubation fibrescope. They too however encountered difficulties due to pooling of oropharyngeal secretion in 30% of their patients, although this did not result in failed intubation.

There are several limitations in this study. Firstly, it was not possible to blind the investigator of the device being used. Nevertheless, all intubations were performed by a single operator with adequate clinical experience using both devices, hence the variability in technique would have been minimized. Presumably, intubation using the Bonfils intubation fibrescope would require greater skill, hence success of intubation is dependent on the capability of the operator. A clinician is considered experienced in using the Bonfils intubation fibrescope after 20 successful intubations with the Bonfils intubation fibrescope. However, Corbanese et al found that the learning curve plateaued only after the 50th intubation. In contrast, the C-MAC videolaryngoscope which is similar in design as the direct conventional laryngoscope requires no or minimal additional skill. The longer intubation time and greater airway manipulation may have also impacted on the hemodynamic changes produced during intubation with the Bonfils intubation fibrescope. Patient awareness accounting for the rise in heart rate, increases with time as delivery of anesthetic gases is suspended during airway manipulation. Another possible limitation is that the airway assessment performed during premedication rounds may have not excluded an unexpected difficult airway encountered in our study.

Future studies on the Bonfils intubation fibrescope could look at the hemodynamic responses during intubation of difficult airways, for which it was intended for. This could determine if the hemodynamic parameters produced during such situations are more comparable with other conventional laryngoscopes or videolaryngoscopes. It would also be useful to study the determinants of tachycardia such as jaw thrust or tongue jaw lift maneuvers, and if this can be reduced by measures such as topical or intravenous local anesthetics.

Summary

This study showed that endotracheal intubation success rates were similar using the Bonfils intubation fibrescope or C-MAC videolaryngoscope. However, intubation time was significantly longer using the former, and resulted in increased heart rates. Nevertheless this did not result in any remarkable clinical consequence on cardiorespiratory parameters amongst healthy ASA I patients.

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HEMODYNAMIC CHANGES: BONFILS VERSUS C-MAC

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A COMPARATIVE STUDY OF THE ANALGESIC EFFECT OF INTRAVENOUS PETHIDINE VS. KETOROLAC AFTER INGUINAL HERNIA SURGERY IN CHILDREN UNDER GENERAL ANESTHESIA

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Introduction: Postoperative pain due to tissue damage caused during surgery not only causes discomfort for the patients, but can also result in prolonged hospitalization, increased morbidity and respiratory disorders, and readmission to the hospital. For postoperative pain control, numerous methods and medications have been suggested, such as non-steroidal anti-inflammatory drugs (NSAIDs) and narcotics. Pethidine, as a narcotic analgesic, and ketorolac, as an NSAID, are widely used for pain control. Thus, in this study, the effects of these two drugs were studied and compared in terms of pain control after inguinal hernia surgery in children of 1-12 years of age.

Materials and Methods: Sixty-six children undergoing inguinal herniorrhaphy were selected and randomly divided into 2 groups. The first group received 0.5 mg/kg ketorolac and the second group received 1 mg/kg pethidine during extubation. Postoperative pain (using Wong Baker pain scale) and complications were measured until 24 hours after surgery.

Results: Mean and standard deviations of postoperative pain 1 hour after surgery in the pethidin and ketorolac groups were 5.06 ± 1.41 and 3.88 ± 0.93, respectively. The scale was significantly lower in the ketorolac group (P <0.001). Postoperative pain intensity 2 hours after surgery in these two groups was 4.48 ± 1.52 and 3.55 ± 1.15, respectively, and the difference between the two groups was significant (P = 0.006). The variation in postoperative pain intensity in the ketorolac group was statistically lower than the pethidin group (P = 0.020).

Conclusion

Keywords: Postoperative pain, ketorolac, pethidin, inguinal hernia surgery

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Introduction

Pain is a defense mechanism induced by tissue damage which causes individuals to react in order to resolve the pain stimulus. Nociceptors are free nerve endings and are stimulated by substances discharged from damaged tissues (such as bradykinin). Postoperative pain due to tissue damage caused during surgery can be the cause of much discomfort for patients. Pain not only affects the body, but also affects the mind and spirit. Prolonged hospitalization, increased morbidity in patients due to lack of mobility and respiratory disorders, and readmission to the hospital can be complications of inadequate postoperative pain control. In addition to having physical and psychological effects, pain also stimulates the sympathetic nervous system and causes side effects such as tachycardia, hypertension, myocardial infarction (MI), hypoventilation, and impaired wound healing.

Effective pain control increases patient satisfaction, reduces the length of hospitalization, and shortens the recovery time after surgery. Moreover, pain is an important criterion for patient satisfaction with physicians and provided treatment operations. Therefore, adequate postoperative analgesia is required and can be provided through different methods, notably prescription of opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and local anesthetics.

Herniorrhaphy in children is associated with postoperative pain that can cause severe distress and complications. The present study aimed to compare the analgesic effect of intravenous pethidine or ketorolac after inguinal hernia surgery in children under general anesthesia.

Materials and Methods

This study was a double-blind clinical trial conducted in 2014 at Alzahra and Imam Hossein Hospitals in Isfahan, Iran. The target population consisted of 1-12 year old children undergoing elective inguinal hernia surgery at the abovementioned centers. Inclusion criteria included patients undergoing elective inguinal hernia surgery, age range of 1-12 years, willingness to participate in the study, lack of psychiatric problems, absence of coagulation disorders and chronic pain syndrome, no history of gastrointestinal bleeding and peptic ulcer, and no history of seizures. It was also decided that in case of any anesthetic and surgical complications that resulted in a change of surgical and anesthetic procedures, such as unexpected increase or decrease in blood pressure, and incidence of dysrhythmia in need of treatment, the patient would be excluded from the study. The required sample size for this study was calculated at 33 patients in each group. This amount was calculated using the sample size estimation formula to compare the two means, and considering the 95% confidence level, test power of 80%, standard deviation of postoperative pain of 1.17, and least significant difference between the two groups of 0.8.

After obtaining the approval of the proposal and the Medical University Ethics Committee, 66 patients, who met the inclusion criteria, were enrolled in the study. To ensure blinding, data was collected by one person and the intervention was conducted by another. Patients were initially administered premedication (intravenous midazolam 0.05 mg/kg), and then, transferred to the operating room, and were placed under general anesthesia using sodium thiopental 5 mg/kg, fentanyl 1-2 μg/kg, and atracurium 0.05 mg/kg. After intubation, anesthesia was maintained with 1-2% isoflurane and a combination of oxygen and N₂O (50%-50%).

After completion of surgery and before extubation, the patients were divided into groups A and B through randomized block method. Group A received 0.5 mg/kg intravenous ketorolac and group B received 1 mg/kg intravenous pethidine. After extubation patients were transferred to the recovery room. In the recovery room, the children’s pain was measured using a standard pediatric pain scale. Based on the Wong Baker pain scale, if the pain intensity was higher than 4, analgesics were prescribed for the patient (preferably 0.5 mg/kg pethidine). In addition, the level of patient’s consciousness was examined after being brought to the recovery room and at 1, 2, 6, 12, and 24 hours after surgery. Hemodynamic parameters...
including blood pressure, pulse rate, all used medications and their possible side effects, such as gastrointestinal bleeding, respiratory apnea, respiratory depression (respiratory rate less than 12 per minute), body rash, and time of first additional analgesic dose administration were recorded. Patients were discharged from the recovery room after regaining full consciousness based on the modified Aldrete score. Furthermore, the incidence of vomiting at the mentioned times were evaluated, and in case of its incidence, 0.07 mg/kg dose of metoclopramide was administered. The total dose of metoclopramide administered in 24 hours in both groups was determined and recorded.

After data collection, the codes were opened by the main executor of the research and the data were analyzed using SPSS software (version 22; SPSS Inc., Chicago, IL, USA). In order to compare the mean of qualitative variables between the groups, independent t-test, and if necessary, Mann-Whitney test were used. To compare the frequency distribution of qualitative variables between the two groups chi-square test was used. Repeated measures analysis of variance (ANOVA) was used to analyze the variation in hemodynamic parameters and pain after surgery. Statistical Significance was considered at P <0.05.

Results

Sixty six children undergoing inguinal hernia operation were randomly divided into two groups of 33 patients each. The mean ages of the groups receiving pethidine and ketorolac were 4.95 ± 2.58 and 4.86 ± 2.59 years, respectively. There was no significant difference between the two groups (P = 0.89). The gender ratios (female/male) in the two groups were, respectively, 28/5 and 30/3, and was not significantly different (P = 0.71). The variation in hemodynamic parameters before surgery until 24 hours after surgery in both groups are illustrated in figs. 1 to 4. Variations in systolic and diastolic blood pressure, mean arterial blood pressure, and pulse showed no significant difference before surgery and until 24 hours after surgery in both groups (P >0.05).
Table 1 shows the mean and standard deviation of consciousness level and postoperative pain intensity in both groups. The level of consciousness on admission to the recovery room and at 1 hour after the operation in the group receiving ketorolac was significantly higher (P < 0.05). However no significant differences were observed in the consciousness level until 24 hours after surgery in the two groups (P = 0.091). Pain intensity and additional analgesics received in both groups are presented in Table 2. The intensity of pain was only different between the two groups at 6 hours after surgery and being lower in the Ketorolac groups. No differences were seen in the additional analgesics received between the two groups.

The time to first narcotic adiminisration, dose of narcotics and metoclopramide were not different between the two groups (Table 3). However, the length of stay in the recovery room was higher in the ketorolac group (Table 3). No postoperative complications were observed in both groups.

Discussion

In the present study, administration of ketorolac reduced pain and the length of stay in the recovery room. In this study, although no significant difference was observed between narcotic dose and the first time of receiving analgesics in the two groups, patients receiving ketorolac used significantly less narcotics and their first analgesics administration time was shorter.

NSAIDs have fewer complications compared to narcotics. Postoperative complications were not observed in any of the patients of the present study. Ketorolac is an NSAID and its anti-inflammatory effect is due to the inhibition of prostaglandin synthesis. Like other cyclooxygenase inhibitors, ketorolac inhibits platelet aggregation, and thus, can increase the risk of bleeding; however, this effect was not observed in the present study. Various

Table 1

The mean and standard deviation of the level of consciousness and postoperative pain intensity in the two groups

<table>
<thead>
<tr>
<th>Time variable</th>
<th>Level of consciousness</th>
<th>Postoperative pain intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pethidine (n =33 )</td>
<td>Ketorolac (n =33 )</td>
</tr>
<tr>
<td>Into Recovery</td>
<td>2.37 ± 0.98</td>
<td>3.63 ± 1.08</td>
</tr>
<tr>
<td>1 hour after surgery</td>
<td>1.72 ± 0.52</td>
<td>1.67 ± 0.5</td>
</tr>
<tr>
<td>2 hours after surgery</td>
<td>1 ± 0.01</td>
<td>1.60 ± 0.24</td>
</tr>
<tr>
<td>6 hours after surgery</td>
<td>1 ± 0.01</td>
<td>1 ± 0.01</td>
</tr>
<tr>
<td>12 hours after surgery</td>
<td>1 ± 0.01</td>
<td>1 ± 0.01</td>
</tr>
<tr>
<td>24 hours after surgery</td>
<td>1 ± 0.01</td>
<td>1 ± 0.01</td>
</tr>
<tr>
<td>P (between the two groups)</td>
<td>0.091</td>
<td></td>
</tr>
</tbody>
</table>
articles have declared different findings regarding the use of ketorolac and its effect on increasing the risk of bleeding during or after surgery. However, in the majority of these studies, no difference was observed between ketorolac and other narcotics regarding increased risk of bleeding\(^\text{15,16}\). For example, ketorolac use in endoscopic sinus surgery is without complications and does not increase the risk of bleeding or anemia due to acute blood loss\(^\text{17}\). In addition, the use of ketorolac in pediatric osteotomy in the lower extremities, pediatric cardiac surgery, scoliosis surgery, and urology surgery has been announced to be without complications and safe\(^\text{7,8,18-20}\). Although some articles showed increase in bleeding\(^\text{21}\) during or after surgery\(^\text{22,23}\), the effectiveness of ketorolac in controlling acute pain after abdominal surgery has been well documented. It has rapid effectiveness and can be used as an analgesic during the surgery and for pain control after surgery\(^\text{24}\). In the study by Kay et al., the use of ketorolac for children undergoing surgery due to bone fracture was without complications; no observations were reported regarding infection and wound problems, or increased risk of delayed bone repair or lack of bone repair\(^\text{25}\).

In many studies, the use of ketorolac after abdominal or pelvic surgery, urological surgery, lumbar decompression surgery, and cesarean section had significant analgesic effects and reduced the need for narcotics\(^\text{5-10}\). In some studies, only a reduction in the need for narcotics was reported. Nevertheless, it did not decrease the duration of hospitalization and returning to oral intake of nutrition\(^\text{26}\). In some studies, in addition to the effectiveness of a single dose of ketorolac in reducing post-operative pain, they also showed that ketorolac reduced nausea and vomiting\(^\text{27}\). Numerous studies have been conducted on the use of analgesics for inguinal hernia surgery. For example, in the study of Lau et al., ketorolac IV before inguinal hernia repair surgery had the same analgesic effect as that of diclofenac suppository\(^\text{28}\). In another study conducted by Splinter et al., in

<table>
<thead>
<tr>
<th>Time variable</th>
<th>Severe pain (higher than 4)</th>
<th>Additional analgesic dosage received</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pethidine (n = 33)</td>
<td>Ketorolac (n = 33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Into Recovery</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1 hour after surgery</td>
<td>15 (45.5%)</td>
<td>13 (39.4%)</td>
<td>0.62</td>
<td>11.25 ± 3.42</td>
</tr>
<tr>
<td>2 hours after surgery</td>
<td>6 (18.2%)</td>
<td>3 (9.1%)</td>
<td>0.48</td>
<td>11.43 ± 4.76</td>
</tr>
<tr>
<td>6 hours after surgery</td>
<td>10 (30.3%)</td>
<td>3 (9.1%)</td>
<td>0.03</td>
<td>10.45 ± 3.5</td>
</tr>
<tr>
<td>12 hours after surgery</td>
<td>2 (6.1%)</td>
<td>3 (9.1%)</td>
<td>0.99</td>
<td>10 ± 0.01</td>
</tr>
<tr>
<td>24 hours after surgery</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups variable</th>
<th>Pethidine (n = 33)</th>
<th>Ketorolac (n = 33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First narcotic admin</td>
<td>1.79 ± 0.42</td>
<td>1.33 ± 0.42</td>
<td>0.45</td>
</tr>
<tr>
<td>Narcotic dosage</td>
<td>8.64 ± 5.53</td>
<td>6.82 ± 5.84</td>
<td>0.20</td>
</tr>
<tr>
<td>Metoclopramide dosage</td>
<td>1.89 ± 0.94</td>
<td>1.62 ± 0.55</td>
<td>0.47</td>
</tr>
<tr>
<td>Length of stay in the recovery room</td>
<td>71.52 ± 12.4</td>
<td>83.48 ± 9.96</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
inguinal hernia repair surgery, the intravenous use of ketorolac was preferred to caudal analgesia. In addition, in the study of Hong et al., preoperative administration of ketorolac for pain relief was effective in inguinal hernia repair in children. In the study by Lieh-Lai et al., the analgesic effects of morphine and ketorolac in children after surgery were compared. They found that the analgesic effect of ketorolac was comparable with morphine, and a single dose of ketorolac did not have an abnormal effect on postoperative bleeding.

In the study by Eberson et al., the effects of ketorolac were examined after pediatric orthopedic surgery. In this study, the ketorolac group had a shorter hospitalization length and showed no bleeding complications. Therefore, they announced that ketorolac was a safe and effective method of reducing postoperative pain. Some studies suggest that narcotics, compared to NSAIDs, have better analgesic effects. In addition, adding ketorolac to narcotics reduced complications and the need for narcotics.

Therefore, based on the results of this study and their comparison to other studies, it can be concluded that ketorolac is effective for pain relief and reduction of complications after inguinal hernia surgery and it is superior to pethidine, and thus, its use is recommended.
References


SHORT-TERM POSTOPERATIVE COGNITIVE FUNCTION
OF ELDERLY PATIENTS UNDERGOING
FIRST VERSUS REPEATED EXPOSURE
TO GENERAL ANESTHESIA

PETROS TZIMAS*, EFSTRATIOS ANDRITSOS**, ELENI ARNAOUTOGLOU***,
GEORGIOS PAPATHANAKOS**** AND GEORGIOS PAPADOPOULOS*****

Background: General anesthesia (GA) may affect cognitive functions and result in postoperative cognitive dysfunction. The aim of our prospective pilot study was to compare the short-term postoperative cognitive function of unimpaired elderly patients undergoing first versus repeated exposure to GA.

Methods: After approval from the Hospital Ethics Committee and informed consent of all participants, 46 patients, 70.1 ± 7.1 years of age, 20 men and 26 women were enrolled in the study. Twenty-five patients belonged to group A (never received GA before) and 21 patients belonged to group B (received at least once GA the last 5 years). Each patient was evaluated preoperatively and the 8th day postoperatively by a blinded examiner with a battery of neurocognitive tests.

Results: Group B patients performed preoperatively worse in Trail Making Test Part A, Stroop Color and Word Test and Three Words-Three Shapes Test. Postoperatively there were differences in almost every neurocognitive test, with group B patients again achieving the worse scores. This came along with increased Beck Depression Inventory Test score and increased incidence of delirium in Group B patients.

Conclusion: Our pilot study suggests that prior exposure of elderly patients to GA might lead to prolonged cognitive impairment and repeated GA exposure seems to be a potential risk factor for greater short-term postoperative cognitive impairment.

Keywords: Cognitive disorders, Anesthesia, Delirium, Dementia, Postoperative complications

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Conflict of interest: The authors declare that there are no conflicts of interest.
Introduction

Studies conducted on non-cardiac surgery have generally agreed that postoperative cognitive dysfunction (POCD) is quite common in the short-term period (up to several weeks after surgery) with no differences between regional and general anesthesia\(^1\)-\(^3\). General anesthesia has differential effects across cognitive domains and POCD in the elderly has been attributed to age-related neuronal changes exacerbated by pharmacotoxic effects\(^4\). Although it is proposed that general anesthesia may demonstrate a cumulative long-lasting detrimental effect on cognitive function of aged patients\(^5\), it is also speculated that repeated exposure to anesthetics might adversely affect long-term performance in quantitative psychometric tests in the elderly\(^7\). The effects of repeated exposure to anesthesia have been studied in experimental models\(^6\)-\(^11\) and repeated anesthesia was recognized as a potential risk factor for the later development of learning disabilities in children\(^12\)-\(^14\). Unfortunately, the studies related to postoperative cognitive function of adult patients after repeated exposure to surgical anesthesia are very few and their results are questionable\(^15\)-\(^19\).

We hypothesized that elderly patients with a past history of general anesthesia present with a greater short-term cognitive impairment after a repeated anesthesia. For that reason we have conducted a pilot study in order to compare the short-term postoperative cognitive function of unimpaired elderly patients undergoing first versus repeated exposure to surgical anesthesia.

Materials and Methods

The Hospital Ethics Committee approved the study protocol for this prospective pilot study and all participants provided their informed consent. The study was conducted during an eighteen-month period, from January 2012 to June 2013. A total of 46 patients aged 60 to 80 years old, scheduled for elective general surgery or an intra-abdominal gynecologic operation under general anesthesia were categorized into two groups according to their past history, i.e. if they had never undergone a surgical procedure under general anesthesia before (Group A, 25 patients) or had received anesthesia at least once in the previous 2 to 5 years (Group B, 21 patients).

Inclusion criteria included patients aged 60 to 80 years old scheduled for elective general surgery or an intra-abdominal gynecologic operation under general anesthesia and scheduled to be admitted to the hospital as an inpatient for a minimum of 8 days after surgery. Participants were required to have Greek as their native language, to have at least an elementary level education and to be able to speak and read fluently in Greek.

We excluded patients if they had any severe visual or auditory disorder; had previously undergone neuropsychological testing; had a Mini Mental State Examination Score (MMSE) <22; had a disease of the central nervous system, e.g. Parkinson’s disease or a previous cerebral vascular event; had a mental disease, alcoholism, drug dependence or were taking tranquilizers or antidepressants; had chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF); were to undergo an emergency surgical procedure or had periprocedural desaturation (≥1 events of \(\text{SpO}_2 < 80\%\) for more than 2 minutes) or were hemodynamically unstable (≥1 events of mean arterial blood pressure ≤60 mmHg for more than 10 minutes).

The preoperative evaluation was performed by an anesthesiologist and information about the patients’ demographic status, medical history, physical examination, type of surgery, ASA classification of physical status, and NYHA functional classification of heart disease were also recorded.

Each patient was evaluated preoperatively and the 8th day postoperatively by a blinded examiner with a battery of neurocognitive tests: Mini Mental State Examination (for grading the cognitive state of patients), Beck Depression Inventory (for assessing the severity of depression), Trail Making Test Parts A and B (for assessing visual conceptual and visuomotor tracking skills), Stroop Color and Word Test (for assessing higher executive function), Controlled Oral-Word Association Test (for detecting changes in word association fluency) and Three Words-Three Shapes Test (for measuring different aspects of learning and memory, including incidental learning, trials to criterion, delayed retrieval and recognition) (Table
The examiner was trained in psychometric test administration and relevant interview techniques by a neuropsychologist. The tests were carried out in the morning, in quiet rooms and only the patient and the examiner were present. In case of reported opioid use due to postoperative pain the previous 24 hours, the psychometric evaluation of the patient was postponed. The patients were evaluated by the 0-10 Numeric Pain Rating Scale (for pain intensity evaluation).

Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini Mental State Examination</td>
<td>Used to screen for cognitive impairment</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>A multiple choice survey for assessing the severity of depression feelings</td>
</tr>
<tr>
<td>Trail Making Test (Parts A and B)</td>
<td>A test of visual conceptual and visuomotor tracking skills</td>
</tr>
<tr>
<td>Stroop Color and Word Test</td>
<td>Used for assessing higher executive function</td>
</tr>
<tr>
<td>Controlled Oral-Word Association Test</td>
<td>A measure of verbal fluency</td>
</tr>
<tr>
<td>Three Words-Three Shapes Test</td>
<td>Provides measures of different aspects of learning and memory</td>
</tr>
<tr>
<td>Confusion Assessment Method</td>
<td>Used for detection of postoperative delirium</td>
</tr>
</tbody>
</table>

Each patient was also evaluated the 2nd to 4th day postoperatively with Confusion Assessment Method for detecting postoperative delirium. The patient was considered delirious if the Confusion Assessment Method was positive on any one of these days.

The surgical operation in both patient groups was performed under general anesthesia. All patients received usual perioperative care, including routine anesthetic and safety monitoring: 5-lead electrocardiography (ECG), blood pressure (BP), oxygen saturation via pulse oximetry (SpO₂), end-tidal carbon dioxide and breathing oxygen. Propofol (2 mg/Kg), fentanyl (1-2 mcg/Kg) and a non-depolarizing muscle relaxant (rocuronium, 0.6 mg/Kg) were used for induction in general anesthesia and sevoflurane 1-2% in air/oxygen mixture together with remifentanil (0.2-0.4 mcg/Kg/min) were used for maintenance of anesthesia. Bispectral Index monitoring (BIS Quatro Sensor, Covidien-Medtronic, U.S.A) was used for estimating the depth of anesthesia and delivery of anesthesia was adjusted to maintain a BIS index of 40-60. Mechanical ventilation used was adjusted to tidal volumes of 6-8 ml/Kg, respiratory rate of 10-12/min, aiming at SpO₂ values >97% and end-tidal carbon dioxide values of about 35 mm Hg. Patients were treated for postoperative pain in order to keep Numeric Pain Rating Scale Score below 3 without any analgesic restriction.

Statistical Analysis

Data is presented as mean and standard deviation (SD). Categorical variables are expressed as number (%). The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous data that was normally distributed was compared using the two-tailed Student’s t-test or, if not, by the Mann-Whitney U-test. Pairwise comparisons were performed using paired Student’s t-test or Wilcoxon test as appropriate. Analysis of categorical data was performed using the x² or Fisher’s exact tests. Significance was defined as a p value of less than 0.05. Analyses were performed using IBM® SPSS® Version 21.

Results

Forty-six patients, 70.1 ± 7.1 years of age, 20 men and 26 women were enrolled in the study. Twenty-five patients belonged to group A (never received general anesthesia before) and 21 patients belonged to group B (received at least once general anesthesia the last 2 to 5 years). No one patient presented surgical complications and there was no need for any patient to be admitted in the intensive care unit postoperatively.

There were no significant differences between two groups considering demographics, American Society of Anesthesiologists (ASA) classification of physical status, New York Heart Association (NYHA) functional classification of heart disease, duration of anesthesia and postoperative value of hemoglobin. However, a significant difference was observed...
Table 2
Demographics, clinical characteristics and operative data. Values are expressed as mean ± standard deviation or number of patients (%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A N. = 25</th>
<th>Group B N. = 21</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.96 ± 7.05</td>
<td>71.43 ± 7.09</td>
<td>0.174</td>
</tr>
<tr>
<td>ASA</td>
<td>1.32 ± 0.48</td>
<td>1.48 ± 0.51</td>
<td>0.285</td>
</tr>
<tr>
<td>NYHA</td>
<td>1.08 ± 0.28</td>
<td>1.19 ± 0.40</td>
<td>0.273</td>
</tr>
<tr>
<td>Preoperative Hb (mg/dL)</td>
<td>12.21 ± 1.44</td>
<td>13.44 ± 1.06</td>
<td>0.006</td>
</tr>
<tr>
<td>Postoperative Hb (mg/dL)</td>
<td>12.42 ± 1.29</td>
<td>13.20 ± 0.91</td>
<td>0.056</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>158.40 ± 39.23</td>
<td>162.86 ± 36.21</td>
<td>0.688</td>
</tr>
<tr>
<td>Hypertension</td>
<td>n = 10 (40.0%)</td>
<td>n = 8 (38.1%)</td>
<td>0.896</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>n = 4 (16.0%)</td>
<td>n = 2 (9.5%)</td>
<td>0.521</td>
</tr>
</tbody>
</table>

Table 3
Comparison of scores of cognitive and pain intensity tests between group A and group B patients, preoperatively and the 8th day postoperatively (mean values ± standard deviation or number of patients (%)).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini Mental State Examination</td>
<td>28.24 ± 1.17</td>
<td>27.71 ± 1.45</td>
<td>0.181</td>
<td>28.20 ± 1.38</td>
<td>25.48 ± 1.08</td>
<td>0.000</td>
</tr>
<tr>
<td>Numeric Pain Rating Scale</td>
<td>0.12 ± 0.33</td>
<td>0.19 ± 0.40</td>
<td>0.512</td>
<td>3.68 ± 0.48</td>
<td>3.62 ± 0.50</td>
<td>0.669</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>78.20 ± 41.37</td>
<td>116.24 ± 73.06</td>
<td>0.029</td>
<td>84.32 ± 47.04</td>
<td>120.48 ± 79.91</td>
<td>0.069</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>202.76 ± 96.70</td>
<td>253.95 ± 97.07</td>
<td>0.081</td>
<td>197.04 ± 106.76</td>
<td>286.05 ± 154.11</td>
<td>0.032</td>
</tr>
<tr>
<td>Stroop Color and Word Test</td>
<td>77.24 ± 19.87</td>
<td>57.81 ± 18.59</td>
<td>0.001</td>
<td>80.28 ± 21.64</td>
<td>59.76 ± 20.45</td>
<td>0.002</td>
</tr>
<tr>
<td>Controlled Oral-Word Association Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Words starting with C</td>
<td>6.68 ± 2.90</td>
<td>7.14 ± 2.39</td>
<td>0.947</td>
<td>6.20 ± 2.75</td>
<td>6.76 ± 3.00</td>
<td>0.671</td>
</tr>
<tr>
<td>Words starting with S</td>
<td>7.12 ± 2.83</td>
<td>6.10 ± 3.45</td>
<td>0.277</td>
<td>6.52 ± 3.19</td>
<td>5.52 ± 3.44</td>
<td>0.122</td>
</tr>
<tr>
<td>Words starting with A</td>
<td>7.12 ± 3.70</td>
<td>5.67 ± 3.38</td>
<td>0.175</td>
<td>6.04 ± 3.54</td>
<td>4.67 ± 4.26</td>
<td>0.140</td>
</tr>
<tr>
<td>Three Words-Three Shapes Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidental recall</td>
<td>24.40 ± 6.01</td>
<td>20.48 ± 6.88</td>
<td>0.045</td>
<td>28.20 ± 2.83</td>
<td>22.14 ± 7.68</td>
<td>0.002</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>22.40 ± 3.85</td>
<td>20.71 ± 4.82</td>
<td>0.345</td>
<td>24.60 ± 4.55</td>
<td>22.38 ± 3.40</td>
<td>0.082</td>
</tr>
<tr>
<td>Beck Depression Inventory Test Score 10-15</td>
<td>n = 3 (12%)</td>
<td>n = 1 (4.8%)</td>
<td>0.391</td>
<td>n = 3 (12%)</td>
<td>n = 8 (38%)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

regarding the preoperative value of hemoglobin between two patient groups, with Group A patients having lower values of hemoglobin preoperatively (p = 0.006) (Table 2).

Between the two patient groups, there were significant differences preoperatively in Part A of the Trail Making Test, the Stroop Color and Word Test, and the Three Words-Three Shapes Test (incidental recall), with Group B patients achieving worse scores (Table 3). In contrast, postoperatively there were significant differences in almost every neurocognitive test (Mini Mental State Examination, Trial Making Test Part B, Stroop Color and Word Test and Three Words-Three Shapes Test, incidental recall), with Group B patients again achieving the worse scores (Table 3).

Three patients in Group A (12%) and 8 patients in
Group B (36.1%) had postoperatively increased Beck Depression Inventory Test scores (p = 0.041).

Delirium, as evaluated using the Confusion Assessment Method, was identified in 5 Group A subjects (20%) and in 9 Group B subjects (42.8%), although not reaching a statistical significance (p = 0.097).

**Discussion**

Based on current medical literature on POCD\(^1\)-\(^3\) and on experimental and clinical observations of cumulative adverse effects of anesthesia\(^6\)-\(^19\), we hypothesized that multiple exposures compared with first exposure to general anesthesia would be associated with greater short-term postoperative cognitive impairment. It was difficult to predict specifically which domains would be affected at most. For that reason we have used pre-and postoperatively a number of different neurocognitive tests in order to examine a broad range of neurocognitive domains.

In our study, preoperatively scores of the Mini Mental State Examination, Trail Making Test Part B, Controlled Oral-Word Association Test and Beck Depression Inventory Test between the two patient groups were statistically non-significant. This finding is consistent with the study of Abildstrom et al found that in non-cardiac surgery patients, POCD if present, has a gradual resolution with cognitive decline being indistinguishable from matched controls at 1 year\(^28\). In the retrospective study of Avidan et al\(^29\), it was found that long-term cognitive decline in older subjects was not attributable to non-cardiac surgery, with the median years of annual follow-up after surgery being 3.1 (1.6-5.5). Furthermore, Ancelin et al\(^4\) showed that 13 months after non-cardiac anesthesia no significant changes in attention, implicit memory, delayed visual memory, verbal fluency and logical series were present.

The unexpected finding of our study was the significantly worse performance of patients with a past history of general anesthesia in Trail Making Test Part A, Stroop Color and Word Test and Three Words-Three Shapes Test at baseline. The Trail Making Test evaluates visual conceptual and visuomotor tracking skills. Stroop Color and Word Test is an instrument for the examination of mental activity variables, concentration effectiveness, cognitive flexibility and executive function, while the Three Words-Three Shapes test (incidental recall) has been proved to be a relatively quick and cost effective way to differentiate between normal and abnormal memory function with aging. This finding strengthens the controversial hypothesis that anesthesia initiates or accelerates subtle lesions leading to more permanent effects and contributes to the development of long-term cognitive decline\(^5\).

Between the two groups there were significant differences in almost every neurocognitive test postoperatively: Mini Mental State Examination, Trial Making Test Part B, Stroop Color and Word Test and Three Words-Three Shapes Test (incidental recall), with group B patients achieving again worse scores. The high rate of delirium recorded in our study is in agreement with previous studies\(^30\). This came along with slightly increased Beck Depression Inventory Test score in group B patients (Table III).

Mini Mental State Examination tests global cognitive functions, including orientation, recall, attention, calculation, language manipulation, and constructional praxis. Trail Making Test Part B is a well validated test to differentiate between normal and pathological aging and requires cognitive flexibility, working memory, set-shifting abilities, the ability to maintain two response sets as well as inhibitory functions\(^31\). This test focuses on not just cognitive processing speed but also considers attention switching difficulties\(^32\).

Although the difference noticed preoperatively in Trail Making Test Part A was not confirmed postoperatively, Trail Making Test Part B is a more reliable tool to identify brain damage and disease and evaluate the status of the brain, regardless of whether the damage is focal or diffuse or the type of pathological involvement\(^33\).

An increased Beck Depression Inventory Test score in group B patients lies in agreement with studies reporting that greater levels of depressive symptoms are associated with greater postoperative cognitive impairment after non-cardiac surgery\(^34\).

The different performance between groups suggests that patients with a past history of general anesthesia present greater short-term cognitive
impairment after repeated anesthesia. The patients with a past history of general anesthesia also presented a greater incidence (almost twice) of postoperative delirium. This difference never reached statistical significance, possibly due to the small number of patients enrolled in our study. Overall, it seems that elderly patients having previously undergone anesthesia at least once prove to be more vulnerable to adverse cognitive effects of general anesthesia.

The higher occurrence of postoperative delirium in cognitively unimpaired elderly subjects may be associated with a worse cognitive outcome and an increased risk of dementia. It is important to note that Trial Making Test Part B is a very common tool used to assess cognitive function in people with possible dementia and executive function in neurodegenerative disorders.

Human studies which examined the link between anesthesia, surgery, and Alzheimer’s disease had conflicting results. An early case-control study showed that neither exposure to six or more episodes of general anesthesia, nor cumulative exposure to 600 min or more of general anesthesia, was associated with an increased risk of Alzheimer’s disease. In another retrospective study, there was no association between the number of procedures or cumulative exposure to anesthesia and development of dementia. A meta-analysis examining the association between general anesthesia and Alzheimer’s disease, showed no significant association between cumulative exposure to general anesthesia and development of Alzheimer’s disease. However, two more recent studies both found an increased incidence of dementia after anesthesia and surgery. It is worth mentioning the existence of a study which concluded that exposure to general anesthesia is inversely associated with dementia; this effect was consistent as a trend with increasing exposure to anesthesia (never general anesthesia: OR = 1.7, 95% CI = 1.1-2.7; one general anesthesia: OR = 1.4, 95% CI = 0.9-2.0; two-five general anesthesias: referent 1.0; more than five general anesthesias: OR = 0.7, 95% CI = 0.3-1.5, P(trend) = 0.003).

Our study should be considered in light of certain limitations. The small sample size of our pilot study cannot detect the precise effect of repeated anesthesia on short-term postoperative cognitive outcome and the clinical evaluation of postoperative short-term cognitive function is biased by the multiple variables that can complicate or characterize the perioperative period. Despite these limitations, this study has several strengths, namely a neuropsychological battery which aimed at detecting changes in the full range of information processing functions. The included patients represent a group of cognitively healthy aged subjects without brain disease and we were able to adjust for a large range of confounding factors (age, gender, depressive symptomatology, cerebrovascular, and cardiac pathology) and perioperative factors (such as pain or depression) which could have led to an underestimation of postoperative cognitive decline. The homogeneity of anesthetic technique and the absence of patients undergoing an emergency procedure is another advantage of our study.

The results of our pilot study support the hypothesis that prior exposure of unimpaired elderly patients to general anesthesia might lead to prolonged cognitive impairment and that repeated exposure to general anesthesia seems to be a potential risk factor for a greater short-term postoperative cognitive impairment. Longitudinal studies will be necessary to clarify the long-term impact of multiple exposures to general anesthesia and surgery on patients’ cognitive status.
References


COMPARISON OF THE EFFECTS OF PREEMPTIVE INTRAVENOUS AND RECTAL ACETAMINOPHEN ON PAIN MANAGEMENT AFTER INGUINAL HERNIORRHAPHY IN CHILDREN: A PLACEBO-CONTROLLED STUDY

GHOLAM REZA KHALILI*, AMIR SHAFA** AND RAMIN YOUSEFI***

Background: Postoperative pain management is a critical concern in pediatric surgery. Acetaminophen is the safest and most widely used analgesic in children. The present study compared the analgesic efficacy of intravenous (IV) and rectal acetaminophen versus placebo in children undergoing inguinal herniorrhaphy.

Methods: A total of 120 children, who were candidate for elective surgical repair of unilateral inguinal hernia, were enrolled and randomly allocated to four groups of 30 patients each to receive IV acetaminophen, acetaminophen suppository, IV placebo, and placebo suppository during surgery. Postoperative pain scores, measured on the Face, Legs, Activity, Cry, and Consolability (FLACC) scale, were recorded and compared.

Results: The four groups had no significant differences in the mean age, weight, length of stay in the recovery room, and duration of operation. The frequency of postoperative vomiting was significantly lower in the IV and rectal acetaminophen groups compared to the two placebo groups (P = 0.04). The mean pain scores of the two acetaminophen groups were similar during the first two hours after surgery. These scores were significantly lower than the scores of the placebo groups. However, the four groups were not significantly different in terms of pain scores at the fourth, sixth, and 12th postoperative hours. During the first hour after surgery, IV acetaminophen had the largest analgesic effect. Moreover, among all four groups, the IV acetaminophen group had the highest sedation level in the recovery room.

Conclusion: Both IV and rectal acetaminophen were more effective than placebo in pain relief after inguinal hernia repair in children. They were also associated with lower frequencies of postoperative vomiting. The greatest analgesic efficacy of both forms was observed during the first two hours after surgery.

Keywords: acetaminophen, suppositories, placebos, herniorrhaphy, groin, analgesia, pediatrics.

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Introduction

Postoperative pain and its complications have long been a concern to surgeons and anesthesiologists. Various methods of perioperative pain management can facilitate patient recovery. Optimal perioperative pain management can consequently reduce postoperative complications, enhance recovery after surgery, and shorten the length of hospital stay. The mechanism of postoperative pain and its related complications necessitates the administration of appropriate pain management strategies by anesthesiologists.

Meanwhile, due to the physiological, pharmacological, developmental, and emotional differences between adults and children, pain management in children is usually challenging. According to available literature, 80% of children experience pain during the first day after a surgical operation. Moreover, the intensity of pain after discharge depends on the requested amount of opioids in the hospital. While pain is a major cause of post-operative agitation, children’s inability to express their feelings generally prevents them from receiving adequate doses of analgesics. In addition to its physiological effects on different body organs, pain can alter the physical and mental states of young children (< five years).

Considering the significance of pain management, preemptive analgesia, first introduced by Crile in the beginning of the 20th century, has received increasing attention. Numerous clinical and experimental studies have confirmed this approach as an efficient pain management strategy with both short- and long-term benefits during the recovery period. A variety of medications, including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen, have been recommended for preemptive analgesia. However, opioids should be strictly avoided since even a single dose of them can increase postoperative vomiting and cause sedation, nausea, and respiratory depression. NSAIDs, on the other hand, may lead to gastrointestinal bleeding and trigger severe asthmatic attacks. Acetaminophen has thus gained growing popularity as a safe analgesic, especially in children.

Acetaminophen is administered in different forms and routes. Several studies have evaluated the effects of acetaminophen rectal suppositories. Razavi et al. compared the effects of acetaminophen suppository and caudal anesthesia on postoperative pain relief in children. Despite similar baseline pain intensity scores of the two groups during the first two hours after surgery, they reported that the acetaminophen suppository group had higher scores over the next hours. In another study, acetaminophen suppository failed to effectively reduce pain after major pediatric surgeries and morphine had to be administered for all patients. The changing and unpredictable bioavailability of rectally administered acetaminophen, ranging between 6.5% and 92.2% in different patients, has been suggested as the reason for the unfavorable analgesic effect of acetaminophen suppositories in postoperative pain relief.

The analgesic effects of intravenous (IV) acetaminophen (paracetamol) has also been widely examined. Murat et al. concluded that propacetamol and Perfalgan injections (two forms of paracetamol) had identical analgesic effects 15 minutes and six hours after herniorrhaphy in children.

It is undoubtedly essential to find a cost-effective analgesic with adequate pain-reducing efficacy. While intravenous and rectally administered acetaminophen have different bioavailability, no research has compared the analgesic effects of these two forms of the medicine. Moreover, previous studies on acetaminophen suppositories have yielded inconclusive results. The aim of the current study is to compare the effects of IV and rectally administered acetaminophen and placebo on postoperative pain in children.

Methods

Upon the approval of the study protocol by the Ethics Committee of Isfahan University of Medical Sciences (Isfahan, Iran), this randomized, double-blind, prospective clinical trial was conducted in Alzahra Hospital and Imam Hossein Pediatric Hospital (Isfahan, Iran) during 2013-14. A total of 120 children who were candidates for elective surgical repair of unilateral inguinal hernia were enrolled. The children were included if they aged six months to 6 years, had no history of allergy to acetaminophen, and were not receiving antiepileptic or sedative drugs. Participants who had perioperative bleeding, underwent prolonged
surgery, and required blood transfusion were excluded. Also, children were also excluded if their inguinal canal was explored.

All patients underwent general anesthesia. While being NPO (nil per os) time, the children received standard maintenance fluids, according to their body weight. In all patients, general anesthesia was induced by the administration of fentanyl 1 - 2 µg/kg, atropine 0.02 mg/kg, atracurium 0.6 mg/kg, and sodium thiopental 5-7 mg/kg. A mixture of 50% oxygen, 50% nitrous oxide, 1.2 minimum alveolar concentration (MAC) isoflurane, and morphine 0.15 mg/kg was also used during anesthesia.

The children were randomly allocated to four groups of 30 patients each. In Groups A and C, general anesthesia was induced and the patients were infused with IV paracetamol (15 mg/kg) and normal saline (15 mg/kg) respectively over 15 minutes before the incision was made. Acetaminophen and placebo suppositories were administered in Groups B and D, respectively.

All procedures were performed by an anesthesiologist not involved in patient assessment.

After the surgery, the patients were transferred to the recovery room and the tracheal tube was removed when the children opened their eyes to command and felt uncomfortable with the tube. The first pain measurement, based on the Face, Legs, Activity, Cry, and Consolability (FLACC) scale, was made immediately after extubation. Pain scores were also recorded 30 minutes and one, two, four, six, and 12 hours after extubation. Modified Aldrete Score was used to decide when the children could be transferred from the recovery room.

The sedation levels of the patients were also determined based on their scores on the Richmond Agitation-Sedation Scale (RASS) and the frequency of receiving additional analgesic medicine (acetaminophen suppository) over the 12-hour period of pain measurement. A trained staff member who was unaware of the administered medicines recorded pain scores, sedation levels, frequency of vomiting, length of stay in the recovery room, and duration of operation in a questionnaire. The questionnaire also contained the patients’ file number, age, gender, and weight.

The collected data were entered into SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and analyzed with chi-square tests and one-way analysis of variance (ANOVA) with repeated measures. P-values less than 0.05 were considered significant.

Results

Patients’ characteristics are presented in Table. There are no statistically significance difference among the four groups.

The four groups had a significant difference in the mean frequency of vomiting during the 12-hour postoperative period (P = 0.04). The two placebo groups (Groups C and D) had the highest frequency of vomiting. However, the slight difference between the frequency of vomiting in Groups A and B was not significant.

Significant differences were observed between the groups’ mean scores of pain immediately after

<table>
<thead>
<tr>
<th>Variable</th>
<th>IV paracetamol (n=30)</th>
<th>Acetaminophen suppository (n=30)</th>
<th>IV placebo (n=30)</th>
<th>Placebo suppository (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>13.56 ± 0.47</td>
<td>13.64 ± 0.61</td>
<td>12.73 ± 0.57</td>
<td>13.02 ± 0.62</td>
<td>0.52</td>
</tr>
<tr>
<td>Age (months)</td>
<td>36.1 ± 20.7</td>
<td>35.3 ± 25.9</td>
<td>32.2 ± 22.6</td>
<td>36 ± 23</td>
<td>0.67</td>
</tr>
<tr>
<td>M/F</td>
<td>25/5</td>
<td>27/3</td>
<td>28/2</td>
<td>24/6</td>
<td></td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>57.6 ± 15.8</td>
<td>56.8 ± 12.7</td>
<td>56.7 ± 12.7</td>
<td>58.7 ± 11.2</td>
<td>0.93</td>
</tr>
<tr>
<td>Length of stay in the recovery room</td>
<td>67 ± 8.7</td>
<td>67.2 ± 13.1</td>
<td>68.3 ± 12.3</td>
<td>68.5 ± 13.2</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Values are n (%).
30 minutes and one and two hours after extubation (P < 0.001) (Table 2). However, no such significant differences were observed at four, six, and 12 hours after extubation (P = 0.43, 0.57, and 0.22, respectively). Patients who received IV paracetamol, followed by those who had acetaminophen suppository, had the lowest pain scores during the first hour after surgery. The two mentioned groups had no significant differences in pain scores over the first two hours after surgery. The two placebo groups had the highest pain scores during these two hours. Their scores, however, were not significantly different (Table 2).

A significant difference in the mean frequency of receiving additional analgesics was seen among the four groups (P = 0.02). The pain scores in the IV paracetamol and acetaminophen suppository groups were similar during the 12-hour period of the study. The values in the two placebo groups were also very not different.

There were significant differences in the mean sedation levels of the four groups. The mean sedation levels in the IV paracetamol, acetaminophen suppository, and the two placebo groups were zero, one, and two, respectively (P = 0.02).

**Discussion**

The present placebo-controlled study examined the effects of preemptive use of IV and rectal acetaminophen on postoperative pain relief in children. The results confirmed both forms of the medicine to have significantly higher analgesic effects compared to placebo. While the greatest analgesic effect during the first hour after surgery was observed in the IV paracetamol group, both forms of acetaminophen had similar and acceptable efficacy in pain relief two hours after surgery. Moreover, the two forms of acetaminophen were as effective in reducing the need for additional analgesics to significantly lower levels compared to the placebo groups. Likewise, vomiting was less frequent in groups receiving acetaminophen than in the two placebo groups. Assessments in the recovery room suggested IV paracetamol to have greater sedative effects in comparison with placebo and acetaminophen suppository.

In one study, Razavi et al. found acetaminophen suppository and caudal anesthesia to have similar efficacy in relieving postoperative pain during the first two hours after surgery. After this period, however, pain scores significantly increased in the acetaminophen suppository group. Heshmati et al. also compared the analgesic efficacy of acetaminophen suppository and pethidine in postoperative pain management in children. While both groups had favorable pain scores (< three) during the first two hours after surgery, the medicines failed to maintain their analgesic effects until the fourth postoperative hour. Consequently, four hours after surgery, pain scores of both groups increased to over three and the patients required additional pain

**Table 2**

*Pain scores measured on the Face, Legs, Activity, Cry, and Consolability (FLACC) scale at different times. Values are presented as mean ± standard deviation.*

<table>
<thead>
<tr>
<th>Time after decannulization</th>
<th>IV paracetamol (n=30)</th>
<th>Acetaminophen suppository (n=30)</th>
<th>IV placebo (n=30)</th>
<th>Placebo suppository (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediately after</td>
<td>0.6 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>2.2 ± 0.3</td>
<td>2.3 ± 0.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>30 minutes</td>
<td>1.2 ± 0.2</td>
<td>2 ± 0.3</td>
<td>2.8 ± 0.4</td>
<td>3 ± 0.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>One hour</td>
<td>2 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>3.5 ± 0.2</td>
<td>3.6 ± 0.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Two hours</td>
<td>2.5 ± 0.2</td>
<td>2.8 ± 0.3</td>
<td>3.3 ± 0.2</td>
<td>3.3 ± 0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Four hours</td>
<td>1.9 ± 0.2</td>
<td>2.1 ± 0.3</td>
<td>2.2 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td>0.43</td>
</tr>
<tr>
<td>Six hours</td>
<td>1.1 ± 0.2</td>
<td>1.3 ± 0.2</td>
<td>1.4 ± 0.3</td>
<td>1.3 ± 0.2</td>
<td>0.57</td>
</tr>
<tr>
<td>12 hours</td>
<td>0.6 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>1 ± 0.1</td>
<td>1 ± 0.2</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Values are mean (SD).*
medication\(^2\). A study in Turkey compared the effects of penile block, caudal block, and IV paracetamol on pain management after circumcision. At the first postoperative hour, pain scores in the penile and caudal block groups were equally lower than that in the paracetamol group. However, no differences were observed between the pain scores of the three groups at 1.5 and 2 hours after the surgery\(^{11}\). A systematic review and meta-analysis by McNicol et al. revealed that 37% of patients receiving IV paracetamol experienced a 50% reduction in pain intensity over four hours (vs. 16% in placebo recipients). Furthermore, the administration of IV paracetamol was associated with a lower need for additional analgesics\(^{12}\). Capici et al. concluded that both IV and rectal acetaminophen had good analgesic effects during the first six hours after surgery. Meanwhile, acetaminophen suppository caused a longer duration of analgesia compared to IV acetaminophen\(^{13}\).

Consistent with previous research, the present study showed acetaminophen to have greater analgesic efficacy compared to placebo. Maximum effects of both IV and rectal forms of the medicine were observed during the first two hours after surgery. This finding can be justified by the half-life (four hours) and the peak effect (one-three hours) of acetaminophen\(^2,14,15\). Despite the effectiveness of both forms of acetaminophen, patients receiving the IV form had higher sedation levels in the recovery room and lower pain scores during the first postoperative hour. This finding is acceptable since acetaminophen suppository has an unpredictable bioavailability (6.5%-92%)\(^9\) and may not be able to increase the plasma levels of the medicine to the required levels\(^9\). Based on available literature, the IV form of acetaminophen achieves its maximum plasma concentrations and penetrates into the central nervous system at an earlier time compared to the other forms of the medicine. Owing to such properties, IV acetaminophen can be regarded as a faster-acting analgesic in comparison to the other two forms of the medicine\(^{16}\).

Heshmati et al. reported postoperative vomiting in 16% of patients who received acetaminophen suppositories\(^2\). The rates varied between 6% and 19% following the administration of IV acetaminophen\(^{17,24}\). Similar frequencies of vomiting were also observed in the present study (10% and 13% in the IV and rectal acetaminophen groups, respectively).

We administered the recommended doses of acetaminophen\(^{13,15}\) and did not measure the serum concentrations of the medicine in the two groups. However, monitoring of serum levels and other pharmacokinetic properties of the medicine can not only clarify the mechanisms involved in different analgesic effects of IV and rectal acetaminophen at different times, but also determine the optimal doses and times of administration.

In conclusion, considering the favorable analgesic efficacy and limited half-life of IV and rectal acetaminophen, maintenance doses of the medicine are recommended for effective postoperative pain management in children undergoing inguinal herniorrhaphy.
References


CASE REPORTS

ANESTHETIC MANAGEMENT DURING COMBINED LIVER AND KIDNEY TRANSPLANTATION

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Abstract

Combined liver and kidney transplantation is a highly demanding and challenging procedure for anesthesiologists due to the lengthy and complicated nature of the procedure, the critical patient condition and the need to balance the intravascular volume to maintain the venous outflow of the hepatic allograft and also the diuresis of the renal allograft. Intravascular volume management and coagulation control, seem to be the most important issues during combined liver and kidney transplantation. There is sparsity of data in the literature concerning the anesthetic and fluid management in CLKT. We present and discuss the anesthetic management in a case series in three patients, who underwent combined liver and kidney transplantation in our institution during the last two years.

Keywords: Liver Transplantation; Kidney Transplantation; coagulation management; fluids management; Prothrombin Complex Concentrate; antifibrinolytic agents.

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Introduction

With advancements in anesthetic techniques, surgical skills and perioperative management, patient survival following liver transplant has been increased considerably, showing a 10 years liver and patient survival above 50%1. It was found that about 18% of the liver transplant patients would suffer from kidney insufficiency requiring dialysis 13 yr after the surgery2. This deterioration of kidney function was attributed to calcineurin inhibitor-induced nephrotoxicity. Furthermore, the adverse influence of decompensated liver on the kidney function among patients waiting for liver transplant has resulted in chronic renal insufficiency in 10-20% of them, and up to 8% receive hemodialysis prior to liver transplant3,4. Pre liver transplant renal dysfunction is an important risk factor for post-operative sepsis, poor outcome and also it will increase the overall cost of transplantation5-6. Moreover, the incidence of renal failure following liver transplant ranges from 12% to 70%7, and if a renal replacement therapy is needed, the mortality rate increases up to 40-90%8. To overcome these problems, there is a more trend to perform combined liver kidney transplant (CLKT).

The United Network for Organ Sharing (UNOS) data revealed that from 2001 to 2006, the number of performed CLKT was almost tripled reaching about 400 CLKT in 20061. This was attributed to the introduction of Model for End-Stage Liver Disease (MELD) scoring system, to allocate donor livers to the patients with a higher risk of mortality on the waiting list of liver transplant, due to the heavily weighted serum creatinine value used in its calculation.

Anesthetic management

Standardized anesthetic technique including general anesthesia and tracheal intubation was used in our patients with some modifications done on case by case basis. After the patient’s informed consent was obtained they were taken to the operating room. Upon arrival, standard monitoring consisting of electrocardiogram, pulse oximetry, and noninvasive blood pressure was established. General anesthesia was induced with 2 mg.kg-1 propofol and 2 mcg.kg-1 fentanyl. Endotracheal intubation was facilitated with 0.2 mg mg.kg-1 cis-atracurium. The patients were mechanically ventilated with oxygen/air mixture keeping arterial carbon dioxide and oxygen tension between 35-40 mmHg and 100-200 mmHg, respectively. Anesthesia was maintained with sevoflurane, continuous infusion of intravenous fentanyl, and neuromuscular blockade with continuous infusion of cis-atracurium. The left internal jugular vein was cannulated, using a triple lumen-central venous catheter for continuous infusion of intravenous medications, bolus fluid administration and continuous central venous pressure (CVP) monitoring. A Swan-Ganz catheter introducer was placed also through the left internal jugular vein for massive volume replacement. The right internal jugular was avoided because of the presence of a dialysis line in the right subclavian vein. The left femoral artery and the left radial artery were cannulated for continuous arterial blood pressure monitoring, arterial blood gases and laboratory sampling. Cell saving was performed and salvaged blood was retransfused to the patients.

Pharmacologic hemodynamic management was achieved with norepinephrine infusion.

Case 1

Female patient (44 years, 149 cm height, 67 kg weight, BMI 30kg/m2) with end stage liver disease (ESLD) due to hepatitis C liver cirrhosis. The patient’s MELD score was 17. A cadaveric hepatic allograft became available but she refused surgery. Renal function rapidly deteriorated, and dialysis was required for 2 months, fitting the criteria for CLKT. The MELD score deteriorated to 40. Another liver and kidney allografts were available, and CLKT was planned. Preoperative laboratory findings were hemoglobin 89 g/L, platelet count 39,000/mm3, white blood cell count 3,400 cells/mm3, international normalized ratio (INR) 3.2, PTT 85 seconds, fibrinogen 0.4 g/L, creatinine 163 µmol/l, electrolytes (K+, Na+, Cl-) within normal range, fasting blood sugar 5.2 mmol/l, and albumin 24 g/l. Preoperative echocardiography and electrocardiogram were unremarkable.
Continuous veno-venous hemodialysis with an output of 250 ml/hour was initiated with the start of surgery. The baseline CVP reading was 9 mm Hg. It was maintained between 5 - 8 mmHg during the preanhepatic, anhepatic phase and neohepatic phases of liver transplant till the start of the renal transplant procedure. Then the continuous veno-venous hemodialysis was stopped and the CVP was slowly increased to 15 mmHg until renal allograft reperfusion using crystalloid hydration with normal saline, and it was kept at this value until urine production was noted. CVP was then gradually decreased again to approximately 10 mmHg until completion of the surgery. Total blood loss was 14 liters. Throughout the surgery, the patient received 21 units (7350 ml) of packed red blood cells, 17 units (3400 ml) of fresh frozen plasma (FFP), 18 units (1260 ml) of platelets, 50 units (1500 ml) of cryoprecipitate, 2500 ml of cell saver blood and 15 liters of normal saline, and produced 120 ml of urine. Additional coagulation management was achieved with single doses of desmopressin (0.3 mcg/kg) and recombinant factor VIIa (rFVIIa) (90 mcg/kg).

**Case 2**

Female patient (54 years, weight 70 kg, height 154 cm, BMI 29.5 kg/m2) with ESLD secondary to cryptogenic cirrhosis, type 2 diabetes mellitus (insulin treated), hypertension, dyslipidemia, hypothyroidism and end stage renal disease (ESRD). The patient’s MELD score was 25. The laboratory evaluation showed hemoglobin 128 g/L, platelet count 103,000/mm3, fibrinogen 2.1 g/L, INR 1.1, PTT 30.9, albumin 31 g/l, electrolytes (K+, Na+, Cl-) within normal range, fasting blood sugar 5.3 mmol/l and creatinine 738 µmol/l. Electrocardiogram showed prolonged QT interval, and echocardiography showed a right ventricular systolic pressure of 40-50 mm Hg with mild tricuspid valve regurgitation.

Continuous veno-venous hemodialysis was on standby. The baseline CVP was 7 mmHg. CVP was maintained between 7-10 mmHg throughout the 3 phases of liver transplant. Then CVP was gradually increased to 18 mmHg one hour before kidney allograft reperfusion and remained at this level until the end of surgery. Blood loss was 3 liters. The patient received 8 units (2800 ml) of packed red blood cells, 4 units (800 ml) of FFP, 10 units (300 ml) of cryoprecipitate, 500 ml of albumin 5%, and 13 liters of plasmalyte. Two grams of tranexamic acid were given intraoperatively.

After completion of the surgery, the patients were transferred to surgical intensive care unit in a stable condition. They all had a smooth post-operative course, with good function of the liver and kidney grafts, except case 2 whose kidney graft did not work properly requiring hemodialysis, but she was discharged home, and only comes to the hospital for her dialysis sessions.
Discussion

Fluid volume management and coagulation control seem to be the most important issues during CLKT. There is sparsity of literature discussing the anesthetic and fluid management in CLKT. In our cases, in agreement with previous study we tried to make fluid management based on literature of isolated liver transplant and kidney transplant.

During kidney transplant, a liberal hydration policy optimizing the cardiac output and renal blood flow is usually employed intraoperatively targeting a CVP between 10 - 15 mm of Hg to decrease the incidence of postoperative renal graft acute tubular necrosis. In contrast, it is believed that maintaining a low CVP limits blood loss during liver resection and orthotopic liver transplant, reducing the need for blood product transfusion and its associated negative impact on postoperative patient outcomes. Although there is no clear evidence for the ideal level during liver transplantation, the CVP is generally maintained between 5-10 mmHg. However, keeping the CVP in the desired range is very difficult in cases where there is both coagulopathy and a need to administer blood products. Additionally, in the CLKT this is obviously controversial, since keeping the CVP low seems to be critical for anesthesia management during liver transplantation, while it has to be increased during renal transplantation.

More controversy comes from that, it has been demonstrated that CVP values <5mmHg could be a reason for hypotension and deterioration of microperfusion in liver grafts.

In our cases we tried to keep the CVP below 10 mmHg during the preanhepatic and the anhepatic phases in accordance with other studies and then CVP was increased to 10 mmHg between the neohepatic phase and 1 hour before the renal allograft reperfusion, where the patients were fully hydrated with crystalloids, with a maximum CVP of 15 mmHg, 17 mmHg and 18 mmHg, in cases 1, 2 and 3 respectively.

During preanhepatic and anhepatic phases, CVP was not allowed to decrease below 5 mmHg. There is increased evidence indicating that CVP values <5 mmHg should be avoided during the anhepatic phase until the end of surgery, since this is associated with elevated creatinine levels, more frequent need for dialysis and increased mortality due to sepsis and graft failure. In contrast, previous studies that Instead of decreasing CVP to an absolute numeric value range, they found that decreasing CVP value 40% from baseline during the anhepatic phase of liver transplant, protected liver function, reduced intraoperative blood loss, and had no detrimental effects on renal function.

In another study comparing CVP above 10 mmHg with CVP below 10 mmHg in the neohepatic phase of liver transplant, the investigators did not find any difference in terms of immediate postoperative allograft function, graft survival, or patient survival. This may support our practice of gradually increasing the CVP in the neohepatic phase in preparation for kidney transplant.

During kidney transplant, hemodynamic stability, better intraoperative renal allograft turgidity, earlier diuresis, and rapid improvement of postoperative renal function, were accomplished with maximal hydration targeting a CVP of 15 mmHg within an hour before renal allograft reperfusion, followed by replacement of urine output targeting a CVP of 8 to 10 mmHg.

Although the CVP was low in case 1, the patient presented significantly increased intraoperative blood loss and increased blood products transfusion. However, the patient had a MELD score 40. This supports considering many factors affecting intraoperative blood loss other than the isolated CVP, like the preoperative patient condition, surgical technique and also the donor parameters (donor risk index).

It is important to note that the CVP is being replaced with newer hemodynamic parameters, such as stroke volume variation (SVV), which may be used to guide fluid management in the patients receiving mechanical ventilation. Despite the superiority of SVV to CVP, the promising results of its use in the patients undergoing liver or kidney transplant are still evolving.

According to the European Renal Best Practice (ERBP) Transplantation guidelines there is no evidence to prefer one type of solution for intravenous volume management of the recipient during kidney transplant surgery, with recommendation to monitor for metabolic acidosis when normal saline is used as the only intravenous fluid in the perioperative period. In our case series we used normal saline for crystalloid...
volume replacement in cases 1 and 2, and Plasmalyte in case 3. There is a report comparing normal saline, lactated Ringer’s and Plasmalyte, in kidney transplants of living related donors. The conclusion was that all three crystalloid solutions can be safely used during uncomplicated, short-duration renal transplants; however, better metabolic profile was maintained in patients who received Plasmalyte27.

Transfusion and coagulation management during CLRT is challenging and coagulopathy is usually multifactorial28. Clinical strategies to reduce blood loss during CLRT include the use of blood products to correct pre-existing or intraoperative coagulopathy. This is achieved by transfusion of fresh frozen plasma (FFP), platelet concentrate, cryoprecipitate and antifibrinolytic agents to correct hyperfibrinolysis that may occur during the procedure28. In our cases the coagulation management was guided by thromboelastography (TEG), performed hourly during the surgical procedure, as well as conventional coagulation parameters. The use of TEG for coagulation management constitutes the more recent trend in coagulation monitoring29-31. A major disadvantage of transfusion of blood products such as FFP is volume overload. To correct a prolonged PT during CLRT several units of FFP are needed, which will result in an increase in CVP and portal (splanchnic) venous blood pressure and in fact will increase the bleeding risk.

Prothrombin complex concentrate (PCC) are hemostatically active highly purified concentrates, prepared from pooled plasma32. They contain all four vitamin K-dependent clotting factors (II, VII, IX and X). In contrast to the traditional infusion of FFP to stimulate coagulation in cirrhotic patients, PCC does not add to the intravascular volume and therefore may be, theoretically, more effective in reducing bleeding complications than FFP infusion32.

It has been demonstrated that hypofibrinogenemia is associated with increased hemorrhage during liver transplantation28. Fibrinogen concentrate is also produced from pooled human plasma. It is stored as a lyophilised powder at room temperature and can be reconstituted quickly with sterile water and infusion volumes are low, allowing for rapid administration without delays for thawing or cross-matching33,34. In many centers, PCC and fibrinogen concentrate are used “off-label” during LT as a rescue therapy during catastrophic bleeding, when coagulopathy is evident. Although the available data on safety in this population does not suggest an increased risk of thrombotic, thromboembolic and ischaemic events associated with PCC and fibrinogen concentrate use, the data are scarce and need to be confirmed in large trials35,36. Currently the first two multicentre, randomized, double-blinded trial comparing the routine use of prothrombin complex concentrate (PCC) or fibrinogen concentrate with a placebo in patients undergoing LT are still pending37,38.

Recombinant factor VIIa (rFVIIa) was used by Busani et al., in a series of seven patients with persistent severe bleeding after application of a standard transfusion protocol, in a dose similar to what we used in case 1 (90 mcg/kg). Blood losses and need for platelets transfusion significantly decreased after rFVIIa administration; a non-significant decrease in red blood cell and fresh frozen plasma transfusions also occurred. In six patients treatment with rFVIIa was effective; only one patient died because of haemorrhagic shock, and no thromboses were detected among the treated patients. The study suggested that in some challenging cases of massive bleeding rFVIIa should be considered as a useful option to control bleeding39.

Tranexamic acid was administrated in case 2, it was given also in case 3. It seems to be the antifibrinolytic agent of choice in liver transplantation, being equally efficacious as the currently unavailable aprotinin. As opposed to a blind prophylaxis with antifibrinolytics in liver transplantation a goal directed therapy, by using thrombelastometry to assess fibrinolysis, has been suggested31,40.

Desmopressin acetate (DDAVP) was used in case 1. Desmopressin increases the levels of factor VIII, vWF, and plasminogen. DDAVP appears to improve blood coagulability during liver transplantation in vitro, possibly by activating coagulation factors and platelets41. In conclusion, CLKT is a highly demanding and challenging procedure for anesthesiologists due to the lengthy and complicated nature of the procedure, the critical patient condition and the need to balance the intravascular volume to maintain the venous outflow of the hepatic allograft and also the diuresis of the renal allograft. Appropriate intraoperative fluid management tailored to each phase of CLRT surgery and targeted coagulation management may have favorable results.
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ANESTHESIA FOR COMBINED LIVER AND KIDNEY TRANSPLANTATION

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TORSADES DE POINTES ASSOCIATED WITH TAKOTSUBO CARDIOMYOPATHY IN AN ANOREXIA NERVOSA PATIENT DURING EMERGENCE FROM GENERAL ANESTHESIA

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Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy, is a disease in which the patient exhibits transient, reversible left ventricular dysfunction that is triggered by physical or emotional stress. Prolongation of QT interval, a risk factor for arrhythmia and sudden death, has been reported to be prevalent among patients with Takotsubo cardiomyopathy and is also observed in those with severe anorexia nervosa. In this report, we describe the rare case of a 30-year-old female patient with anorexia nervosa who developed Torsades de Pointes associated with Takotsubo cardiomyopathy during emergence from general anesthesia for emergency exploratory laparotomy.

Keywords: Torsades de Pointes, Takotsubo cardiomyopathy, Anorexia nervosa, General anesthesia.

Introduction

Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy, is a disease that exhibits an acute left ventricular apical ballooning associated with physical or emotional stress. There are increasing case reports of patients who developed Takotsubo cardiomyopathy in the perioperative period because of the stress of anesthesia and a surgical procedure. Prolongation of QT interval, a risk factor for arrhythmia and sudden death, has been reported to be prevalent among Takotsubo cardiomyopathy patients. Prolonged QT interval also appears in severe anorexia nervosa patients. In this report, we describe a rare case of a young woman with anorexia nervosa who presented with Torsades de Pointes (TdP) associated with Takotsubo cardiomyopathy during emergence from general anesthesia.

Case report

A 30-year-old woman patient (height 160 cm, weight 43 kg) was brought to our hospital in an ambulance with self-inflicted neck, left upper arm, and abdominal wounds. Her medical history included alcoholic liver injury for one year and anorexia nervosa for 10 years. Physical findings included thinness, abdominal distension with ascites, and leg edema. Laboratory data...

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showed anemia (hemoglobin 9.4 g/dL), liver dysfunction (total bilirubin 1.7 mg/dL, aspartate aminotransferase 58 U/L, lactate dehydrogenase 261 U/L, γ-glutamyltranspeptidase 70 U/L, and prothrombin time 17.2 s), malnutrition (cholinesterase 55 U/L, total protein 4.8 g/dL, and albumin 1.9 g/dL), and electrolyte imbalance (Na 134.7 mEq/L, and K 3.16 mEq/L). The electrocardiogram (ECG) performed on admission showed QT prolongation measuring 497 ms in the QTc interval (Fig. 1).

![Fig. 1](ECG on admission showed QTc prolongation (QTc 497 ms). Bazett’s formula was used to correct QT interval)

The patient was scheduled for emergency exploratory laparotomy. Preanesthetic medication was not administered. On arrival in the operating room, her blood pressure was 108/65 mmHg, heart rate was 132 beats per minute (bpm), and peripheral oxygen saturation was 96% on room air. General anesthesia was induced with intravenous remifentanil (0.3 µg/kg/min), propofol (40 mg), and rocuronium (25 mg), and endotracheal intubation was performed. Anesthesia was maintained with oxygen (1 L/min), air (2 L/min), sevoflurane (1.0%), remifentanil (0.15-0.25 µg/kg/min), and intermittent dose of fentanyl (total 100 µg). Neuromuscular blockade was maintained with intermittent rocuronium. The patient was monitored with ECG, noninvasive blood pressure measurement, capnography, pulse oximetry, and the bispectral index (BIS). The patient’s intraoperative systolic blood pressure was 80–100 mmHg, heart rate was 85–105 bpm, and BIS was 40–55. Careful review of intraoperative ECG revealed QTc prolongation (QTc 613 ms), probably because of the decrease of heart rate (Fig. 2). Surgery, which lasted for 55 min, was performed uneventfully. Intraoperative total blood loss was 50 ml, urine output was 50 ml, and total infusion volume was 800 ml. At the end of surgery, sugammadex 200 mg was administered for the reverse of muscle relaxation. Approximately 5 min after reversal, TdP degenerating into ventricular fibrillation ensued (Fig. 3). External cardiac massage was immediately performed, and 2% lidocaine (100 mg) and adrenaline (1 mg) were administered. After DC shock (200 J), she recovered sinus rhythm. An arterial blood gas analysis showed pH, partial pressure of oxygen (PaO₂), and partial pressure of carbon dioxide (PaCO₂) of 7.354, 545.2 mmHg, and 38.6 mmHg, respectively. The serum potassium concentration was 3.08 mEq/L, and other serum electrolytes were within normal limits. A transthoracic echocardiogram performed in the operating room revealed the akinesis of the apical segment, preserved basal function, and reduced left ventricular function (35% ejection fraction), which are consistent with Takotsubo cardiomyopathy (Fig. 4).

![Fig. 2](Intraoperative ECG showed remarkable QTc prolongation (QTc 613 ms))

The patient was transferred to the intensive care unit (ICU). The QTc interval on ICU admission was 499 ms (Fig. 5). The correction of hypokalemia and a continuous infusion of intravenous amiodarone were provided to treat arrhythmia. Although the QTc prolongation persisted even after hypokalemia correction, further TdP or ventricular fibrillation was not observed. However, she developed massive ascites with liver dysfunction, and the control of massive ascites was difficult. A large dose of catecholamine (dopamine, dobutamine, and noradrenaline) was continuously administered, but the patient’s hemodynamic status remained unstable with systolic blood pressure at approximately 60–70 mmHg. The patient died one day after surgery.
TDP ASSOCIATED WITH TAKOTSUBO CARDIOMYOPATHY IN ANOREXIA NERVOSA

Discussion

Takotsubo cardiomyopathy is characterized by reversible left ventricular dysfunction, chest pain or dyspnea, ECG alterations (i.e., ST segment elevation and T wave inversion), and only modest elevations of serum levels of cardiac enzymes and troponin. Moreover, significant organic stenosis or spasm of a coronary artery is not usually detected in the coronary angiography.

It has been reported that reversible left ventricular dysfunction is precipitated by physical or emotional stress. Although the exact mechanism of Takotsubo cardiomyopathy remains unclear, it has been suggested that activation of cardiac adrenoceptors is the primary cause of this syndrome. Moreover, Takotsubo cardiomyopathy has higher incidence in elderly females, and it is rare in young premenopausal women; thus, a decrease in estrogen may be involved in the development of this syndrome.

There are increasing case reports of Takotsubo cardiomyopathy during the perioperative period, likely due to the stress of anesthesia and a surgical procedure. Most of these cases are reported during induction of anesthesia or in the postoperative course after procedures such as cholecystectomy, total gastrectomy or electroconvulsive therapy. However, there are few reports that occurred during emergence from general anesthesia. Shin et al. presented a case of Takotsubo cardiomyopathy after percutaneous endoscopic lumbar discectomy under general anesthesia, confirming that seizure activities after general anesthesia may lead to a higher risk for Takotsubo cardiomyopathy.

Malignant arrhythmia in the setting of Takotsubo cardiomyopathy has been reported. This includes ventricular fibrillation, ventricular tachycardia, atrial fibrillation, and atrioventricular block. Gianni et al. reviewed a total of 286 patients with Takotsubo cardiomyopathy and reported that cardiogenic shock (4.2% of the patients) and ventricular fibrillation (1.5%) were not infrequent. In addition, according to a report by Syed et al., there were 15 reported cases of ventricular fibrillation [prevalence of 1.8% (15 of 816 cases)], 10 cases of sustained ventricular tachycardia [prevalence of 1.2% (10 of 816)], 38 cases of atrial fibrillation [prevalence of 4.7% (38 of 816)], and 24 cases of atrioventricular block [prevalence of 2.9% (24 of 816)]. Therefore, these reports suggest that ventricular arrhythmia is clinically important in Takotsubo cardiomyopathy, although it is considered that malignant arrhythmia is less likely to occur in Takotsubo cardiomyopathy than in acute myocardial infarction. Furthermore, Torsade de Pointes, a potentially life-threatening ventricular arrhythmia has been reported in association with Takotsubo cardiomyopathy. Although the prevalence of QT interval prolongation among patients with Takotsubo cardiomyopathy is high, TdP has been reported less frequently in these patients.

Fig. 4
Transthoracic echocardiogram during systole revealed left ventricular ballooning (double arrow) and hyperkinesis of basal segments (single arrow)

Fig. 5
ECG on ICU admission showed QTc prolongation (QTc 499 ms)
with Takotsubo cardiomyopathy was first reported by Denney et al.\textsuperscript{15} and subsequently by several other authors\textsuperscript{16,17}. In that report, Denny et al.\textsuperscript{15} reported that Takotsubo cardiomyopathy could be considered among the causes of long QT syndrome and TdP. However, we could not find any report of TdP associated with Takotsubo cardiomyopathy in the perioperative period. This is the first case of TdP related to Takotsubo cardiomyopathy during emergence from general anesthesia.

As mentioned above, it is well recognized that physical or emotional stress cause Takotsubo cardiomyopathy. It is therefore possible that emotional stress and the stress of anesthesia and a surgical procedure can cause Takotsubo cardiomyopathy, which in turn can lead to QT interval prolongation. On the other hand, it is known that factors such as hypokalemia, bradycardia, or antiarrhythmic drugs can prolong the QT interval and may induce TdP. Since the QTc interval on ECG obtained approximately 4 years earlier had been normal (QTc 444 ms), an acquired cause of QT prolongation was suspected. In the present case, QT interval prolongation was induced by hypokalemia and Takotsubo cardiomyopathy and subsequently resulted in TdP.

Furthermore, the patient had suffered from anorexia nervosa during the preceding 10 years. Several cardiovascular complications, such as QT interval prolongation or arrhythmia appear in patients with severe anorexia nervosa\textsuperscript{9}, and a high proportion of deaths in these patients are due to cardiac arrhythmia\textsuperscript{18}. There are several reports on the association of Takotsubo cardiomyopathy with anorexia nervosa\textsuperscript{19,20}. Rotondi et al.\textsuperscript{20} reported a case of a woman with anorexia nervosa showing evidence of Takotsubo cardiomyopathy complicated by recurrent TdP. In that report, the authors concluded that the QT prolongation caused by Takotsubo cardiomyopathy was apparently amplified by anorexia nervosa and resulted in malignant and recurrent ventricular arrhythmias. Therefore, it is thought that the QT interval prolongation in our patient was amplified by anorexia nervosa in the same way as the previous reported case. It has been reported that sevoflurane induces significant QT interval prolongation\textsuperscript{21-23}. By contrast, propofol is considered to be less likely to prolong QT interval\textsuperscript{21,23}. Therefore, propofol may be a more appropriate anesthetic for patients with anorexia nervosa.

The present case demonstrates that TdP associated with Takotsubo cardiomyopathy can occur during emergence from general anesthesia. Furthermore, QT interval prolongation may be enhanced by anorexia nervosa.
References


PERIOPERATIVE CARE OF A CHILD WITH CRISPONI SYNDROME

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Crisponi syndrome is an autosomal recessive disorder characterized by intermittent episodes of muscular contraction of the facial muscles with trismus and excessive salivation simulating a tetanic spasm. These episodes occur in response to tactile stimulation or during crying. Associated physical and constitutional findings include characteristic facial anomalies, camptodactyly, intermittent hyperthermia, and feeding difficulties. We present a 15-month-old girl who required anesthetic care during laparoscopic fundoplication and gastric tube insertion. The perioperative implications of the disorder are reviewed and suggestions for anesthetic management provided.

Introduction

Crisponi syndrome was first described in a cohort of 17 patients from a total of 12 families1. It is an autosomal recessive disorder that is characterized by the neonatal onset of episodes of marked muscular contraction of the facial muscles with trismus and excessive salivation simulating a tetanic spasm2. These episodes occur in response to tactile stimulation or during crying. Additional features include characteristic facial abnormalities, intermittent hyperthermia, and feeding difficulties1. It is usually lethal during the first year of life1. We present a 15-month-old girl who required anesthetic care laparoscopic fundoplication and gastric tube insertion. The perioperative implications of the disorder are reviewed and suggestions for anesthetic management provided.

Case report

Institutional Review Board approval is not required at King Fahad Medical City (Riyadh, Saudi Arabia) for publication of isolated case reports. A 15-month-old, 9.2 kilogram girl presented for laparoscopic fundoplication and gastrostomy tube insertion. Associated problems included generalized hypotonia, swallowing difficulties, GERD, recurrent respiratory infections, dysmorphic facial features as noted in Fig. 1 (rounded face, poorly developed and depressed nasal bridge, anteverted nares, long philtrum, high-arched palate and micrognathia), low-set ears, cubitus valgus with flexion deformities at the elbows, intermittent contracture of the facial muscles, puckering of the lips, and drooling of foamy saliva when crying. Past medical history included dilated...
cardiomyopathy secondary to sepsis with a respiratory infection 5 months ago. The patient’s cardiac function had improved since then and she was on no cardiac medications and recent echocardiogram showed normal function. One month ago, hydrocephalus was noted on computed tomography imaging and a ventriculoperiopotentential shunt was inserted. She also had mild thoracolumbar scoliosis with an angle of 20° (Fig. 2). The child was the product of a full term gestation, delivered by Cesarean section due to breech presentation with history of a consanguineous marriage. The only other sibling died had died suddenly during infancy, having been diagnosed with Crisponi syndrome. Medications included domperidone 2 mg per nasogastric (NG) tube every 6 hours, omeprazole 10 mg per NG once a day, flutamide 50 µg via metered-dose inhaler (MDI) every 12 hours, and albuterol via MDI every 6 hours. Vital signs included a heart rate of 120 beats/minute, blood pressure of 100/52 mmHg, a room air oxygen saturation of 96%, respiratory rate of 28 breaths/minute, and a temperature of 37°C. The patient had a 24 gauge intravenous cannula in place. She was transported to the operating room and standard American Society of Anesthesiologists’ monitors were placed. Anesthesia was induced with the inhalation of sevoflurane in 100% oxygen. After effective bag-valve-mask ventilation was demonstrated, propofol (2 mg/kg) and ketamine (2 mg/kg). Endotracheal intubation was performed on the first attempt with a 4.0 cuffed ETT using indirect laryngoscopy (Glidescope®). Neuromuscular blockade was then provided using a single dose of rocuronium (0.5 mg/kg). A second peripheral intravenous cannula and a radial artery cannula were inserted. Anesthesia was maintained with sevoflurane (expired concentration of 2-3%) and fentanyl 4 µg/kg. Surgical duration was approximately 2 hours. Estimated blood loss was minimal. Intraoperative fluids included 130 mL of lactated Ringer’s solution. At the completion of the procedure, residual neuromuscular blockade was reversed with neostigmine and the patient’s trachea was extubated. Postoperative analgesia was provided by morphine and paracetamol (15 mg/kg) with infiltration of bupivacaine 0.25% at the port sites. She was admitted to the Pediatric ICU for postoperative observation of her respiratory status. She was discharged to the inpatient ward after 24 hours and was discharged home on postoperative day 7. Her postoperative course was unremarkable.

**Discussion**

Crisponi syndrome is a rare autosomal recessive syndrome, described in 1996 by Crisponi, which is caused by mutations in the CRLF1 gene. It has been reported in fewer than 30 patients from 13 Italian families, most from Sardinia and is generally lethal during the first year of life. Although postulated to be a distinct syndrome, similarities exist between the Crisponi phenotype and Freeman-Sheldon syndrome, the severe form of Schwartz-Jampel type 2, and Stuve-Wiedemann syndrome (SWS). The phenotype is characterized by muscular contractions at birth, facial abnormalities (chubby cheeks, broad nose with anteverted nares, and long philtrum as noted in Fig. 1), camptodactyly (Fig. 3), and episodes of unexplained hyperthermia. Early in the neonatal period, patients with Crisponi syndrome develop continuous hyperthermia unrelated to infectious or other etiologies,
respiratory manifestations including dyspnea, apnea, and cyanosis during crying\textsuperscript{1,6}. Abnormal central control of respiration may result in sudden death\textsuperscript{1,6}. Following the first year of life, febrile episodes may disappear while feeding difficulties persist.

Fig. 3
Campylodactyly with flexion deformity at the elbow

Crisponi syndrome can be confirmed by testing for mutations in the genes cardiotrophin-like cytokine factor 1 (CLCF1) or cytokine receptor-like factor 1 (CRLF1)\textsuperscript{1-3}. These two proteins function together to form a unit known as the CRLF1/CLCF1 protein complex. This complex attaches to a receptor protein known as the ciliary neurotrophic factor receptor (CNTFR) on the surface of many types of cells. When the CRLF1/CLCF1 protein complex is bound to CNTFR, it triggers signaling within the cell that affects cell development and function. Defects of the proteins coded by CLCF1 and CRLF1 disable the CNTFR signaling pathway. At least four different mutations in the CLCF1 gene have been reported to cause cold-induced sweating syndrome resulting in hyperthermia and disorders of body temperature regulation\textsuperscript{2-4}. The CNTFR pathway's involvement in motor neuron and bone development provides clues to the other signs and symptoms of Crisponi syndrome including distinctive facial features, facial muscle weakness, and skeletal abnormalities\textsuperscript{1-3}.

As with all anesthetic care, appropriate preoperative preparation begins with a thorough history and physical examination. Patients with known genetic syndromes pose a variety of challenges to the anesthesia provider including the potential for difficulties with airway management\textsuperscript{7}. To date, there are no previous reports regarding the anesthetic care of patients with Crisponi syndrome; however, given the phenotypic facial features as noted in our patient (micrognathia and a high-arched palate), potential difficulties with bag-valve-mask ventilation or endotracheal intubation should be anticipated. The appropriate equipment for dealing with the difficult airway should be readily available prior to anesthetic induction\textsuperscript{8,9}. As was performed in our patient, general anesthesia can be induced by the incremental inhalation of sevoflurane in 100% oxygen with the maintenance of spontaneous ventilation until effective bag-valve-mask ventilation is demonstrated\textsuperscript{10}. Once effective bag-valve-mask ventilation was demonstrated, the depth of anesthesia was deepened with the administration of ketamine and propofol followed by indirect laryngoscopy and endotracheal intubation using the Glidescope\textsuperscript{11}. Airway management may be further compromised by the risk of aspiration due to gastroesophageal reflux which may suggest the need for rapid sequence intubation (RSI). However, the use of RSI must be weighed against the risks of potential difficulties with airway management and endotracheal intubation.

Regardless of the etiology, hypotonia may affect perioperative care, impacting decisions regarding the use of neuromuscular blocking agents (NMBAs), especially with regards to the safety of using succinylcholine\textsuperscript{12}. Given the lack of previous reports regarding anesthetic care of patients with Crisponi syndrome, there are no data on which to base recommendations regarding the use of succinylcholine. Given the anticipated duration of the procedure and clinical circumstances, rocuronium was chosen for our patient. Given the intraoperative requirements for the surgical procedure, a low dose of rocuronium (0.5 mg/kg) was effective without the need for repeated dosing. No prolongation of effect was noted and neuromuscular blockade was reversed completely at the completion of the procedure with neostigmine. However, non-depolarizing NMBAs should be used with care as the effect can be prolonged even with routine dosing in patients with pre-existing neuromuscular diseases or hypotonia\textsuperscript{13,14}. Alternatively, where available, sugammadex may provide an additional margin of safety for reversal of the neuromuscular blocking effects of rocuronium or vecuronium\textsuperscript{15}.
The majority of patients with Crisponi die in the neonatal period or in early childhood. Recurrent episodes of unexplained hyperthermia unrelated to exposure to anesthetic agents are the cause of death in most cases. Cold-induced sweating develops usually at a later age. The pathogenesis of hyperthermia is complex. Once the body temperature reaches a critical level (>41.5°C), heat stress activates an acute-phase response with systemic inflammation and coagulation disturbances\textsuperscript{16}. This results in multi-organ system failure including encephalopathy, rhabdomyolysis, acute renal failure, and disseminated intravascular coagulation\textsuperscript{16-18}. Many different disease processes, environmental situations, and systemic stresses can initiate this response. Avoidance of stimuli known to cause hyperthermia and active maintenance of euthermia are important considerations in preventing critical hyperthermia and its fatal consequences. Abnormal central control of respiration with apnea has been reported in patients with Crisponi syndrome\textsuperscript{19}. This finding, autonomic dysfunction with hyperthermia, paroxysmal muscular contractions, and trismus suggests supports the hypothesis of brainstem dysfunction as the etiology of sudden death in Crisponi Syndrome.

One additional perioperative concern is the potential for postoperative respiratory dysfunction and failure. Chronic or acute aspiration may result in respiratory dysfunction which may be potentiated by associated hypotonia and abnormal central control of ventilation. As such, close monitoring of postoperative respiratory function is suggested, preferably in an ICU setting. While effective pain control is essential, associated respiratory and central nervous system involvement may predispose these patients to respiratory depression with opioids. As such, adjunctive agents including non-opioid analgesics (paracetamol) and local/regional anesthesia are suggested to limit perioperative opioid requirements\textsuperscript{20}.

Crisponi syndrome is a rare autosomal recessive disorder that was first reported in the literature in 1996. Given the associated feeding difficulties, anesthetic care may be required for fundoplication or placement of a gastroscopy tube. Potential perioperative concerns include phenotypic features which may make airway management challenging, spontaneous episodes of profound hyperthermia, brainstem dysfunction with defective central control of ventilation, hypotonia, and chronic lung disease related to aspiration.
References


LOEYS-DIETZ SYNDROME: PERIOPERATIVE ANESTHESIA CONSIDERATIONS

JUDY G. JOHNSON*, JACOB P. BRAY**, WILLIAM H. RISHER**, ALAN DAVID KAYE*

Loeys-Dietz syndrome (LDS) is a rare autosomal dominant disease related to genetic mutations in receptors for the cytokine transforming growth factor-receptor type 1 (TGFB-R1) or 2 gene (TGFB-R2) on the cell surface. LDS results in abnormal protein synthesis and dysfunctional connective tissue, which can result in unique cardiovascular anesthesia challenges related to perioperative management. Patients with LDS may manifest hypertelorism, bifid uvula or cleft palate, and arterial tortuosity. Virtually all LDS patients show some type of abnormal skin findings and bleeding tendency. These patients may show a rapid progression of aortic dilation, regurgitation, and a propensity towards rupture and/or dissection at a much earlier age and smaller aneurysm size. LDS patients who require surgical intervention require meticulous vigilance from the anesthesiologist. We describe a 26 year old patient with documented LDS type 1 who presented for repair of an ascending/root aneurysm in this case report. Recognition of LDS and intra-operative management of the cardiovascular manifestations of this disease is paramount in ensuring successful surgical outcome and to limit morbidity and mortality.

Introduction

Loeys-Dietz syndrome (LDS) is an aggressive connective tissue disease leading to potential life-threatening aortic aneurysms. Genetic mutations leading to abnormal protein synthesis and poor development of the body’s connective tissue lends to some features similar to Marfan syndrome. However LDS has some unique physical characteristics that set it apart from other connective tissue disorders. Phenotypic abnormalities described as hypertelorism, bifid uvula or cleft palate, and arterial tortuosity can manifest in these patients. Almost all patients show some type of abnormal skin findings including translucent skin, soft or velvety skin, easy bleeding, easy bruising, recurrent hernias, and scarring problems. Mutations in receptors for the cytokine transforming growth factor-receptor type 1 or 2 gene have been identified as the etiology. It is important to distinguish between Marfan’s syndrome and Loeys-Dietz syndrome because there are a few management differences. LDS patients may show a rapid progression of aortic dilation, regurgitation, and a propensity towards rupture and/or dissection at a much earlier age and smaller aneurysm size. Surgical intervention necessitates teamwork between many different specialties often including the cardiologist, surgeons, nursing, and in particular, meticulous vigilance on the part of the anesthesiologist. Comprehensive care of patients with LDS involves a wide scope of knowledge, support, counseling, and education.

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Case Report

We describe a 26 year old patient with documented LDS type 1, who presented for repair of an aortic arch aneurysm. One year previously, she underwent endovascular coil embolization of 3 of 4 gastric aneurysms. Access to the fourth aneurysm had proven to be technically challenging and not feasible. Upon review of her medical history, she complained of a history of migraines, hypertension and joint hypermobility. The patient stated that her abdominal pain had improved throughout the year following embolization. No family history of connective tissue disease was elicited. Hypertelorism and a repaired bifid uvula were noted in her past medical history. Craniosynostosis and cervical spine instability were not present. Diagnostic imaging previously revealed a right to left shunt per TTE bubble study, a tortuous left vertebral artery, numerous splanchnic artery aneurysms and a 37mm aortic root measured at the sinus of Valsalva. Selective angiogram a year prior demonstrated complete thrombosis of the common hepatic artery. Arterial inflow to the liver was noted at that time as via retrograde flow from the gastroduodenal artery via the pancreaticoduodenal arterial network. The patient had been placed on the angiotensin receptor antagonist Losartan at the time of her embolization. She was followed with serial U/S imaging of her aorta with high suspicion that surgical repair was imminent. Over the course of 12 months, her proximal aorta had increased in size to 41mm via TEE. Cardiac catheterization revealed normal coronaries, a sinus of Valsalva of 48mm, an ascending aorta of 3.17 cm with mild aortic insufficiency. Prophylactic surgical repair was recommended.

The day prior to surgery, the cardiothoracic surgeon relayed to the anesthesiologist, in depth, the nature of the patient’s medical condition and the plan for surgical repair. The surgeon had questioned the patient at length about her desire for additional children and had counseled her extensively about the risks of any future pregnancies.

A detailed anesthetic pre-operative assessment was performed with emphasis placed on the patient’s blood pressure, C-spine, airway, and cardiac status. Her height was 1.70 meters, weight 66Kg, with a calculated BMI of 22.8. EKG, C-spine films and CXR were normal. Vital signs: 130/90, HR 82, RR 22, and Temp of 98.7 F. Airway examination was documented as a Mallampati I with good extension and flexion of the cervical spine.

Details of the anesthetic plan including all intravenous access and prolonged intubation were explained to her. PFT’s and baseline ABGs were noted to be normal. The patient was pre-medicated with Midazolam 2 mgs prior to entering the operating room. An additional 4 mg of Midazolam and 100mcg of Fentanyl was titrated during right radial arterial line placement along with a pulmonary artery catheter (48cm) via the right internal jugular vein. Ultrasound guidance was used during access of the internal jugular. All systemic and pulmonary artery pressures were within normal limits with SV02 readings around 80%. After thorough pre-oxygenation, induction was performed using Etomidate 10 mg, Fentanyl 250mcgs, 100mg of 2% Lidocaine and 100mg of Succinylcholine. Intubation was accomplished without difficulty using a conventional laryngoscope with a Miller 2 blade. Additional maintenance was provided with Sevoflurane 2% in oxygen.

There were minimal cardiovascular responses to intubation or sternal splitting and no abnormal bleeding was seen intraoperatively. Purse strings were placed in the arch of the aorta and right atrium. The patient was given heparin intravenously. Intra-op TEE revealed the ascending aorta at the sinuses to be 48mm in size, and described as “very thin walled”. Aortic and vena cava cannulas were placed. The patient was placed on cardiopulmonary bypass (CPB) and the aorta cross clamped. Antegrade and retrograde cardioplegia was given every 15 to 20 minutes. Buttons on the right and left main coronary arteries were made. A 10mm Hemaseel graft was sewn end to end to the left main and brought posteriorly. The aortic valve leaflets were excised and a 29 mm St. Jude valve conduit was seated, sewn and tied into place. An end graft to the ascending aorta just proximal to the innominate was performed. The Cabrol was brought around to the right side of the ascending aorta and sewed end-to-side to the valsalva portion of the graft. The button of the right coronary was sewn directly into the valsalva portion. The patient was weaned off CPB with the support of
Epinephrine at a dose of 5mcg/min and Milrinone at a dose of 0.25mcg/kg/min. Pulmonary artery pressures were 20-29/13-15mmHg with a Cardiac Index of 3 to 3.5 L/min/m² post CPB. TEE monitoring showed an adequate valve repair along with adequate myocardial contractility. Biatrial and Biventricular leads were placed and the chest was closed in routine fashion. She was weaned off the epinephrine continuous infusion and extubated approximately 4.5 hours later. The patient’s post-operative course was uneventful. Coumadin therapy was initiated. All lines were removed on post-op day 1. She was transferred to the floor post-op day 2 and discharged home on Post-op day 5.

Discussion

Molecular and pediatric geneticists, Dr. Harry Deitz, set out to understand the mechanisms behind aneurysm syndromes. Through genetically altered mouse models, he was able to reveal new and unanticipated processes that were driving connective tissue syndromes such as Marfans. Marfans syndrome is a deficiency in the protein fibrillin-1. This deficiency leads to enhanced activation of the TGF-B molecule, which then stimulates the cells by binding to a receptor (TGF-B-R) that sits on the cells surface. This enriched TGF-B stimulation of the cells leads to many features of Marfans such as dislocation of the lens of the eyes, overgrowth of long bones, low fat stores and weak tissues.

Throughout his research of aneurysmal syndromes, Dr. Dietz found that many genes for other connective tissue diseases are really all funneling down a single pathway, the TGF- B pathway. In 2005, Dr. Dietz and his colleague Dr. Bart Loeys described a new syndrome known as Loeys-Dietz. The natural history of this syndrome is characterized as being more aggressive than Marfans, having unique physical markers and higher risks of aortic tear at an earlier age. Initially 2 types of LDS were distinguished; however, a continuum of the disease with variability in the gene mutation leading to differing physical attributes has been recognized. Four forms or types of LDS have been identified:

**Type 1 (OMIM #609192)** - Patients present with typical craniofacial features i.e., cleft palate/bifid uvula, craniosynostosis and/or hypertelorism. The triad of hypertelorism, palate/bifid uvula and arterial aneurysm/tortuosity is most specific for this type. These patients are more likely to have cardiovascular surgical interventions at younger ages. A shorter life span exists in type 1 LDS patients left untreated.

**Type 2 (OMIM #608967 & #610380)** - Patients have milder craniofacial features, but exhibit skin abnormalities such as velvety translucent skin, bruising and atrophic scarring, and joint laxity.

**Type 3 (OMIM #61375)** - Patients have a mutation in protein SMAD3 which was initially described as the aneurysm-osteoarthritis syndrome. Currently classified as LDS type 3, these patients exhibit craniofacial abnormalities similar to type 1. Radiographic evidence of osteoarthritis can be seen as early as age 12.

**Type 4 (OMIM #614816)** - TGFβ2 mutations are implicated in Marfan syndrome and LDS patients. The clinical phenotype shows features similar to Marfan patients; bifid uvula, mitral valve disease, club foot, aortic aneurysm, and skeletal signs. These individuals seem to have a high incidence of cerebral manifestations such as stroke, cerebral aneurysm, and
subarachnoid hemorrhage.

Most likely, in the past, many patients with LDS may have been diagnosed with Marfans. It is important to distinguish between Marfans syndrome and Loeys-Dietz syndrome because there are subtle differences both with symptoms and treatment (Table 1).

Although, specific phenotypic features are noted and categorized into various types, much overlap is seen. One common theme throughout the continuum of LDS is the predisposition to aggressive vascular disease, leading to dilatation and to dissection of vessel walls. LDS is associated with a high risk of arterial rupture or dissection. Abdominal aortic aneurysms have been identified in 10% of patients, while head and neck aneurysms occur in 10% of patients. Additional clinical features of the two syndromes are presented in Table 2.

<table>
<thead>
<tr>
<th>Table 1</th>
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<td>Comparison of Marfans versus LDS</td>
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<table>
<thead>
<tr>
<th></th>
<th>Marfans</th>
<th>LDS type 1</th>
<th>LDS type 2</th>
<th>AOS/LDS type 3</th>
<th>LDS type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype defect</td>
<td>fibrin1</td>
<td>TGFβ-R1 or TGFβ-R2</td>
<td>TGFβ-R1 or TGFβ-R2</td>
<td>SMAD 3</td>
<td>TGF-b2</td>
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<tr>
<td>Inheritance</td>
<td>AD</td>
<td>AD</td>
<td>AD</td>
<td>AD</td>
<td>AD</td>
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<tr>
<td>Age</td>
<td>Childhood through Adulthood</td>
<td>Childhood-20s</td>
<td>Teens-20s</td>
<td>Middle age adult but can be early teen</td>
<td>30s-40s</td>
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In order to understand connective tissue disorders, it is imperative to understand that cell behaviour is regulated by growth factors that activate transmembrane receptor kinases. Enzymatic cascades that regulate gene transcriptions are initiated by substrates of these kinases. Although growth factors have specific receptors, the pathways can be highly interconnected. The transforming growth factor beta (TGFβ) signaling pathway is one such pathway. It is involved in many cellular processes of developing embryos and also growth in adults. TGF-B regulates cell growth, cell differentiation, apoptosis and cellular homeostasis. Intracellular proteins known as SMADs phosphorylate this TGF-B ligand which is essential for extracellular signals to traverse the cell and gain entry to the nucleus. These proteins in the nucleus then up or down regulate gene expression.

In addition, intracellular effectors such as Erk 1 and Erk 2 phosphorylate an array of transcription factors, in order to regulate cells. (Davies et al, 2005) noted that Erk activation, and Smad signalling are both necessary for TGF-β-induced epithelial-mesenchymal transformation, a key event in neoplastic invasion and metastasis. Activation of Erk is necessary for TGF-β induced fibroblast replication.

During the past 2 decades, research has shown that genetic factors play a key role in the formation of thoracic aortic aneurysms. Dysregulation of the transforming growth factor (TGF)-B signalling pathway has been identified as the key culprit in the pathogenesis of thoracic aortic aneurysms. The majority of individuals with Loeys-Dietz syndrome are diagnosed with aneurysms. Aneurysms not only occur at the aortic root, but may be found throughout the arterial tree. Dissections have occurred at smaller aortic root diameters (4 cm), and at potentially younger ages as opposed to other connective tissue diseases such as Marfans (5cm). Clinically, type 1 patients seem to have a worse prognosis when compared to type 2 patients and usually present earlier at the time of their first cardiovascular surgery (mean age 16.9 years versus 26.9 years) and die younger (mean age 22.6 years versus 31.8)². It is important in these patients to have both timely diagnosis and prompt imaging. Surgical intervention of aneurysms to prevent life-threatening vascular events is often warranted. Valve-sparing aortic root replacement surgery may be recommended to avoid the need for anticoagulation based on the degree of involvement.

These recommendations have been implemented by the vast majority of cardiovascular societies.¹³

- Patients with Loeys-Dietz syndrome should undergo complete aortic imaging at initial diagnosis and 6 months thereafter to establish if enlargement is occurring.

- Patients with Loeys-Dietz syndrome should have yearly magnetic resonance imaging from the cerebrovascular circulation to the pelvis.

- It is reasonable to consider surgical repair of the aorta in all adult patients with Loeys-Dietz syn-
drome or a confirmed TGFBR1 or TGFBR2 mutation and an aortic diameter of 4.2 cm or greater by transesophageal echocardiogram (internal diameter) or 4.4 to 4.6 cm or greater by computed tomographic imaging and/or magnetic resonance imaging (external diameter).

This goes along with the premise of gene-tailored management leading to recommendations of prophylactic surgery based on underlying genetic makeup. LDS patients with a mutation in TGFBR1, TGFBR2 or SMAD3 should be a surgical candidate when the ascending aorta reaches 40 to 42 mm diameters by echocardiogram. However, the TGFBR2 patients seem to have milder aortic disease, and this group of patients is small with specific treatment guidelines under review.2,5.

Despite recommendations that patients with LDS undergo extensive surveillance at a young age, knowledge and awareness of this newly described syndrome may not be established. In the case of our patient, she had been referred from a vascular surgeon, outside the institution, who failed to establish a clear diagnosis of LDS.

Cervical-spine instability has been observed in about 15% of individuals with LDS. Pre-operatively, C-spine imaging, both in the flexion and extension positions should be evaluated as it may impact anesthetic management especially during intubation. A small proportion of individuals with LDS require cervical fusion surgery to stabilize their spine.3,4.

Female LDS patients are at increased risk of obstetric complications and genetic counseling is necessary. There is a high risk of aortic dissection or uterine rupture during pregnancy and the immediate postpartum period.2,14 Many women with LDS have had successful pregnancies. It is unfortunate that there are no predictors to better identify which women may potentially experience complications. Beta blocker usage is often maintained throughout pregnancy for hemodynamic control. Early delivery and elective Cesarean section to reduce high intra-abdominal pressure, and reduce the risk of complications are often employed. Though intuitive, there is an absence of studies comparing the efficacy of cesarean and vaginal deliveries.15 However, Dr. Dietz points out that the vast majority of aortic tears occur a few weeks after delivery, and that performing Cesarean sections did not seem to prevent aortic ruptures from occurring. The question of what starts at the end of pregnancy, and is maintained after delivery is the hormone oxytocin. Oxytocin stimulates uterine contraction, and also milk letdown in the postpartum period. Oxytocin is sustained during breastfeeding, and mediates its effects on peripheral tissues through Erk activation. Through mouse models of MFS, Habashi et al. found a response to oxytocin receptor expression upregulation in the aorta during pregnancy and estrogen release. 96% of the mice died in pregnancy due to aortic rupture. Mice pups separated from the mothers, resulted in a 70% female survival rate. Therefore the natural hormone, oxytocin may not be good in LDS individuals. The FDA approved drug Atosiban, which inhibits preterm labor, also blocks oxytocin and may prove to be helpful in preventing aortic growth.20.

Dural ectasia has been identified in connective tissue diseases such as Marfan’s and Elher’s Danlos and LDS. Regional anesthesia has been performed on these patients for labour and Cesarean section. However, Lacassie et al. describe two cases of Cesarean section where subarachnoid anesthesia failed to provide adequate surgical analgesia.16 The authors attribute this patchy block to an increased lumbosacral CSF volume. The erratic spread of spinal anesthesia in both of these cases was most likely the result of dural ectasia and increased CSF volume.16.

Our G4P2 patient had previously undergone extensive genetic testing, leading to a diagnosis of LDS, after giving birth to a premature dysmorphic appearing child. An IUD had been placed in our patient, but subsequent symptoms of increased abdominal pain prompted removal. She had previously been counseled extensively regarding risk of pregnancy.

Medical therapy had been aimed at decreasing wall stress and tension within the aorta by using antihypertensive agents such as Beta blockers and ACE inhibitors. Losartan, an angiotensin receptor antagonist, has been shown to improve aortic wall architecture along with slowing the rate of aortic dilation in Marfan mice.5,17-18,19 The angiotensin pathway is a regulator of the TGF-B pathway. Thus, the strategy of utilizing Losartan as a means to arrest aneurysmal growth has been studied.5,5 Losartan is not just lowering blood
pressure, but blocking the TGF-B activity. Lacro et al are conducting an ongoing multi-center clinical trial in humans to compare outcomes in individuals with MFS randomized to either atenolol or losartan\textsuperscript{21}. Losartan has relatively low side effects; however, the drug has the potential for fetal toxicity.

The assumption that all blood pressure medications are good for these syndromes may not be accurate. Calcium channel blockers in mouse models have shown aggressive increases in aortic wall thickness by activation of Smad and Erk. This activation of the TGR-B pathway may propagate aggressive growth of an aneurysm\textsuperscript{22}.

As with the case of our patient, hemodynamic stability during the intra-operative period in order to minimize sheer stress and aortic wall tension is of utmost importance. It has been shown previously that general anesthesia can be successful in these patients often using a “balanced” approach of narcotic therapy along with inhalational agents. Our general anesthetic technique was effective in preventing tachycardia and hypertension in this patient.

In conclusion, Marfan and LDS mouse models have helped with the development of treatments to prevent aneurysms from forming for the lifetime of the mouse. Through this advanced research, geneticists continue to unravel the mysteries on TGF-beta signaling, and the potential treatment role of TGF-beta antagonists.

Physician awareness of this disease is critical due to the aggressive nature of the disease, and high risk of mortality and morbidity. Anesthesiologist will be faced with challenges related to this new syndrome. Exposure will occur not only in the operating room but also in the labor and delivery suites. Recognition of various treatment modalities for blood pressure management, obstetric pain management, and perioperative risks should be foremost on the anesthesiologist mind. Recognition of LDS and intra-operative management of the cardiovascular manifestations of this disease are of utmost importance. Parents, families and individuals affected with Loeys-Dietz syndrome may seek support and guidance from multiple specialists including their anesthesiologist.
References


Skin reactions following the application of electrocardiography (ECG) electrodes have been reported in adults and children, and are postulated to result from contact with the conductive gel or adhesive used on the electrodes. Although contact dermatitis is the usual cause of such reactions, contact depigmentation or hypopigmentation may also occur. We report a case of hypopigmentation in a healthy boy following continuous electrocardiography monitoring during general anesthesia for dental rehabilitation.

Introduction

Contact dermatitis due to the conductive gel or adhesive found on electrocardiography (ECG) electrodes has been reported in adults and children\(^1\)\(^-\)\(^4\). Since continuous ECG monitoring is an American Society of Anesthesiologists (ASA) standard for anesthesia care, every child having general anesthesia is at risk for developing a skin reaction to the placement of ECG electrodes. We report a case of hypopigmentation in a child following ECG electrode placement for monitoring during anesthesia.

Case Report

After institutional review board (IRB) approval and parental consent, we reviewed the case of a healthy 4-year-old boy with no known drug or food allergies who underwent a dental rehabilitation under general endotracheal anesthesia. Standard monitoring was performed, including the placement of three ECG electrodes (Kendall Medi Trace 530\(^\circ\)) over the chest. Continuous ECG monitoring was performed for about 1 ½ hours during the procedure. General anesthesia was provided using sevoflurane and nitrous oxide, and there was supplementation with intravenous fentanyl, propofol, dexamethasone, and ondansetron. The procedure, anesthetic, and recovery were uneventful, and the boy was discharged to home in stable condition with no documentation of cutaneous inflammation or lesions in the post anesthesia care unit (PACU). About one month after the procedure, the mother noticed three hypopigmented circular areas corresponding to the size, shape, and location of the ECG electrodes that had been placed during anesthesia. There was no preceding or concurrent erythema, scaling, or rash reported by the mother. She documented the lesions with photographs.
(Fig. 1) and contacted the anesthesiologist. She was referred to a pediatric dermatologist for evaluation, but the lesions slowly resolved over the subsequent months before the appointment, so the skin exam was normal at that visit. The dermatologist performed no diagnostic studies and prescribed no treatment.

**Discussion**

Reports regarding skin reactions (erythema, pruritis, hypopigmentation, and hyperpigmentation) to the conductive gel and adhesive in ECG electrodes have been published1-5. One report includes a similar case of hypopigmentation without preceding erythema in a 29-year-old woman, with subsequent spontaneous resolution5. Contents of conductive gel implicated in these skin reactions have included cross-linked polymers (propylene glycol), acrylates, and p-tert-butylphenol-formaldehyde1,3,4. The adhesive surrounding the conductive gel has also been implicated in some reactions. P-tert-butylphenol-formaldehyde may be found in both the adhesive and gel components of the electrode1. Contact dermatitis may take hours to days for onset after contact and days to weeks for resolution. Although hyper- or hypopigmentation can follow contact dermatitis, this case was unusual because no visible inflammation was reported to precede the hypopigmentation of the skin. In addition, the lesions had a delayed onset of about one month and lasted several months before spontaneous resolution. The patient’s mother was a nurse and frequently bathed the child, making it unlikely she overlooked significant erythema or pruritis.

Other possible diagnoses were considered due to the lack of preceding symptoms. Since there was no antecedent inflammation, we believe contact hypopigmentation rather than post-inflammatory hypopigmentation from an allergic or irritant contact dermatitis was the most likely etiology. Contact hypopigmentation can be due to either induced vitiligo or a direct chemical toxic effect on the melanocytes. The latter is more likely, as the patient has not developed other lesions of vitiligo, the lesions appeared hypopigmented rather than depigmented, and he had not displayed other autoimmune tendencies6. Pityriasis alba, a mild form of eczema, may also present with self-limited hypopigmented lesions, but these should not appear with sharp, geometrically defined borders that correspond with external contacts, and lesions are usually on the upper outer arms and cheeks in patients with atopic dermatitis7. Tinea versicolor, a superficial fungal infection, can produce lesions with a similar appearance, but does not present with a few isolated lesions corresponding to prior contact8.

Anesthesiologists should be aware that skin

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*Fig. 1*

*Photograph of patient taken by mother about one month following procedure*
ECG-ELECTRODE INDUCED HYPOPIGMENTATION

reactions may occur in children following placement of ECG electrodes. The usual diagnosis is contact dermatitis that is self-limited with removal of the offending agent. Mild erythema and pruritis can be treated with topical steroids and oral diphenhydramine. Patients with persistent post-inflammatory or contact hypopigmentation should be referred to a dermatologist for evaluation. Other persistent, severe, or unusual reactions may reflect a more serious underlying medical condition, and should also prompt consultation with a dermatologist. Families should inform future medical caregivers of such a reaction so that exposure can be limited during care.

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PERIOPERATIVE CARE OF AN INFANT WITH GOMEZ-LOPEZ-HERNANDEZ SYNDROME

ONUR BALABAN* AND JOSEPH D. TOBIAS**

Gomez-Lopez-Hernandez syndrome, also known as cerebello-trigeminal dermal dysplasia, is a rare neurocutaneous syndrome classically characterized by the triad of rhombencephalosynapsis, trigeminal anesthesia, and bilateral parietal alopecia. Associated clinical features include a characteristic facial appearance (mid-face hypoplasia, hypertelorism, and low-set, posteriorly rotated ears), brachycephaly, strabismus, ataxia, developmental delay, short stature, and corneal opacities. Given the associated congenital anomalies, anesthetic care may be required for various surgical interventions. We report a 7-month-old with Gomez-Lopez-Hernandez syndrome scheduled for laparoscopic gastrostomy with tube placement and frenulotomy under general anesthesia. The potential perioperative implications of such patients are reviewed and options for anesthetic care discussed.

Introduction

Gomez-Lopez-Hernandez syndrome (GLH) syndrome, also known as cerebello-trigeminal-dermal dysplasia was reported by Gómez in 1979 and subsequently by López-Hernández in 1982. GLH syndrome is one of the more uncommon neurocutaneous syndromes, with only 30 cases reported in the literature since its initial description in 1979. The classical triad of clinical findings includes rhombencephalosynapsis, trigeminal anesthesia, and bilateral parietal or parieto-occipital alopecia. Rhombencephalosynapsis is the most characteristic malformation seen in GLH syndrome. It is characterized by posterior fusion of the cerebellar hemispheres and by agenesis or hypogenesis of the vermis, fusion of the dentate nuclei, and apposition or fusion of the cerebellar peduncles. Additional clinical features of GLH syndrome may include craniofacial anomalies such as brachycephaly or brachyturricephaly, a distinct facial appearance (midface hypoplasia, hypertelorism, and low-set, posteriorly rotated ears), strabismus, ataxia, developmental delay, short stature, and corneal opacities secondary to trigeminal anesthesia. As no chromosomal abnormalities have been determined using karyotyping or subtelomere screening, it is postulated that de-novo chromosomal arrangements or spontaneous dominant mutations are responsible for the clinical findings. Given the associated congenital anomalies, anesthetic care may be required for various surgical interventions. We report a 7-month-old male with Gomez-Lopez-Hernandez syndrome scheduled for laparoscopic gastrostomy with tube placement and frenulotomy requiring general anesthesia. The potential perioperative implications of such patients are reviewed and potential anesthetic regimens discussed.

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There were no conflicts of interest to be declared for any of the authors.
Case Report

Institutional Review Board approval is not required by Nationwide Children’s Hospital for presentation of single case reports. The patient was a 7-month old, 5.9 kg infant presenting for laparoscopic gastrostomy with tube insertion and frenulotomy due to feeding difficulties and failure to thrive. The patient was diagnosed with Gomez-Lopez-Hernandez syndrome during the neonatal period based on findings from brain magnetic resonance (MR) imaging and the characteristic physical features. He was delivered as twin B at 37 weeks gestation via Cesarean section. Routine ultrasound examination at 20 weeks gestation had shown the abnormal brain structure. Pregnancy was complicated by a bicornuate uterus and a velamentous insertion of the umbilical cord. Birth weight was 2640 grams with Apgars of 9 and 9. The patient was born to a 27 year old mother and a 32 year old father. The medical history of the mother included dyslexia and attention deficit disorder. She was also found to have Factor V Leiden deficiency and treated with enoxaparin during pregnancy. She took prenatal vitamins and there was no known exposure to tobacco, alcohol, drugs, or other teratogens. The patient’s 2 year old brother was being evaluated for possible autism. Continuous positive airway pressure (CPAP) was required for approximately 12 hours after delivery due to respiratory distress. Post-delivery karyotype and microarray tests were normal. MR imaging of the brain revealed rhombencephalosynapsis (RES). He had abnormal movements including head shaking/rolling, motor developmental delay, and bilateral parietal alopecia. Associated co-morbid conditions included feeding problems, gastroesophageal reflux, diarrhea, and failure to thrive. The patient’s past surgical history included two lingual frenulotomies. Medications at the time of his current surgery included ranitidine, albuterol, lansoprazole, hyoscyamine, and multivitamins. There were no known allergies. His pre-operative vital signs included a resting respiratory rate of 36 breaths/minute, an oxygen saturation of 97% by pulse oximetry on room air, a heart rate of 121 beats/min, and a blood pressure (BP) of 97/51 mmHg. Preoperative physical examination revealed an abnormal head shape and nystagmus. There were no clinical signs of respiratory and cardiovascular dysfunction. Airway examination revealed congenital ankyloglossia and a Mallampati Class II view. Preoperative laboratory evaluation including electrolytes, renal function, and blood glucose were normal. The patient was admitted on the day of surgery. He was held nil per os for solids for 6 hours and for clear liquids for 2 hours prior to surgery. The patient was transported to the operating room and routine American Society of Anesthesiologists’ monitors were placed. Nitrous oxide (50%) in oxygen was administered via the face mask for one minute. Anesthesia was then induced with sevoflurane. No anticholinergic agent was administered prior to anesthetic care. The baseline heart rate was 120 beats/min with a blood pressure (BP) of 105/75 mmHg. The concentration of sevoflurane was increased by 2% every 3-4 breaths to a maximum inhaled concentration of 8%. Because of the patient’s non-reassuring airway examination, no neuromuscular blocking agents were administered. Spontaneous ventilation was maintained throughout induction and endotracheal intubation. Light cricoid pressure was applied, which brought the vocal cords into view (Cormack-Lehane score of 1). Endotracheal intubation was easily achieved using a Miller 1 blade and a cuffed 3.5 endotracheal tube. The patient tolerated anesthetic induction and endotracheal intubation without adverse effects. Mechanical ventilation was initiated for the case. Maintenance anesthesia consisted of sevoflurane (end tidal concentration 2-3.5%) in 50% oxygen and air, dexmedetomidine (0.3 μg/kg), and fentanyl (2.5 µg/kg). HR decreased from 152 to 128 beats/min and mild hypotension occurred after the administration of fentanyl, which did not require therapy. The blood pressure stabilized between 70-80/30-40 mmHg during the case. The surgical procedure lasted approximately 1.5 hours. There were no intraoperative surgical complications. A total of 120 mL of lactated Ringer’s solution was administered during the procedure. Wound infiltration was administered by the surgeon for postoperative analgesia using 3 mL of 0.25% bupivacaine with 1:200,000 epinephrine. The patient was transported to the Post-Anesthesia Care Unit (PACU) and his trachea was extubated uneventfully in the PACU. He was hemodynamically stable, spontaneously breathing, and discharged from the PACU without any complications. The remainder of the postoperative course was uneventful.
Discussion

Patients with known genetic syndromes may pose a variety of challenges to the anesthesia provider\(^6\). As with all anesthetic care, appropriate preoperative preparation begins with a thorough history and physical examination. Of primary concern to the anesthesia provider in patients with diagnosed or potential genetic syndromes is the potential for difficulties with airway management and endotracheal intubation related to craniofacial abnormalities including micrognathia, midface hypoplasia, and other associated dysmorphic features. The appropriate equipment for dealing with the difficult airway including an indirect videolaryngoscope should be readily available prior to anesthetic induction or airway management\(^7,8\). As was accomplished in our patient, general anesthesia can be induced by the incremental inhalation of sevoflurane with the maintenance of spontaneous ventilation until the airway is secured or adequate bag-valve-mask ventilation is demonstrated. In many instances, endotracheal intubation can be accomplished without the use of neuromuscular blocking agents with sevoflurane supplemented with intravenous propofol or an opioid (remifentanil) if needed. Despite the dysmorphic features noted in our patient, airway management was not complicated and direct laryngoscopy with minimal cricoid pressure provided a grade I view of the glottic structures.

To date, there has been only one previous publication regarding anesthetic care for patients with GLH syndrome, which involved the provision of general anesthesia for a 2-year-old girl during MR imaging of the brain\(^9\). Given the dysmorphic facial features, the authors were prepared for a potentially difficult airway prior to anesthetic induction as a GlideScope® and equipment for fiberoptic endotracheal intubation were available. Similar to our case, anesthesia was induced with the inhalation of sevoflurane and the maintenance of spontaneous ventilation. During anesthetic induction, upper airway obstruction occurred with persisted despite placement of an oral airway. A laryngeal mask airway (LMA) was placed which resulted in the resolution of upper airway obstruction. The LMA was left in place for the imaging procedure. Spontaneous anesthesia was maintained and anesthesia provided by a propofol infusion at 7.2 mg/kg/hour (120 µg/kg/min). No perioperative issues were noted. In their review, the authors identified several potential features which may impact perioperative care including potential airway concerns, psychiatric and behavioral problems (hyperactivity, depression, and self-injurious behavior), trigeminal anesthesia with recurrent corneal and facial scarring, parietal scalp alopecia, muscular hypotonia which may result in upper airway obstruction, as well as ventriculomegaly and the potential for hydrocephalus.

The cognitive performance of patients with GLH syndrome may range from moderate-severe impairment to normal cognitive function\(^8,10\). Baseline mental and intellectual impairment should be assessed to help differentiate pre-existing problems from postoperative complications. Documentation of neurologic deficits is suggested prior to anesthetic care. Symptoms such as hyperactivity, depression, self-injurious behavior and bipolar disorder may require premedication or sedation. Careful postoperative observation and protection should be employed to avoid self-injury in behavioral disorder cases.

Given the potential for trigeminal anesthesia, one of the major concerns regarding perioperative care is protection from damage to the insensate areas including the cornea. Although trigeminal anesthesia is considered one of the classic triads of GLH syndrome, it is not invariably present\(^10\). As cognitive performance permits, the presence of trigeminal anesthesia should be documented. Corneal ulcerations, clouding, keratitis, or facial scarring related to trigeminal anesthesia may be present preoperatively and should be carefully documented during the preoperative examination\(^11\). Corneal abrasions may result from direct trauma to the unprotected eye during anesthetic induction and airway management or more commonly during the postoperative period especially in patients with altered cognitive function and hyperactivity issues. Loss of pain perception and inhibition of protective corneal reflexes may further increase the risk of corneal injury\(^12\). As such, careful attention to corneal protection is suggested during perioperative care.

Scalp alopecia in GLH syndrome was originally described as bilateral parietal or occipital non-scarring alopecia, but it may present in many other distributions\(^13\). As alopecia may be hidden by surrounding scalp hair,
it is important to document the areas of alopecia to ensure differentiation from a possible pressure-related complication due to prolonged positioning in the operation room setting.

Given the invariable involvement of the central nervous system, hypotonia is invariably present inpatients with GLH syndrome. Involvement of the upper airway with dyscoordination of the pharyngeal musculature may result in upper airway obstruction during anesthetic induction. This is also relevant during the perioperative period when the effects of residual anesthetic agents and neuromuscular blocking agents may exacerbate poor baseline function and result in perioperative respiratory insufficiency. Muscular hypotonia can also impact on postoperative respiratory function at the level of upper airway and the thoracic musculature and diaphragm. As was chosen for our patient, the use of short acting anesthetic agents should be considered. In many cases, neuromuscular blocking agents are not required even for endotracheal intubation. These patients may also require prolonged postoperative care in a monitored setting following major surgical procedures. Although no such problems were noted in our patient, the previous report of anesthetic care noted upper airway obstruction during anesthetic induction that was not relieved by placement of an oral airway, but was resolved with insertion of an LMA.

Hydrocephalus may coexist with developmental anomalies of central nervous system. Ventriculomegaly with the development of hydrocephalus has been reported in GLH syndrome as well as rhombencephalosynapsis. Clinical signs and symptoms of increased intracranial pressure should be identified during the preoperative assessment.

In summary, patients who have GLH syndrome may present for diagnostic imaging or various surgical procedures requiring general anesthesia. The current report is only the second in the literature to provide guidance regarding the anesthetic care of such patients. Potential perioperative implications include a potentially difficult airway given the associated dysmorphic features of the head and face, psychiatric and behavioral problems (hyperactivity, depression, and self-injurious behavior), trigeminal anesthesia with recurrent corneal and facial scarring, parietal scalp alopecia, muscular hypotonia, as well as ventriculomegaly and the potential for hydrocephalus.
References


Charcot-Marie-Tooth disease comprises a group of disorders characterized by progressive muscle weakness and wasting. Reviewing the anaesthetic literature produced conflicting reports about the best anaesthetic options for patients with CMTD; as they are at increased risk of prolonged response to muscle relaxants, malignant hyperthermia and risks of regional anaesthesia. We present a case of the successful use of total intravenous anaesthesia with dexmedetomidine and propofol combined with caudal block using bupivacaine mixed with dexmedetomidine without any complications, for a 17 year old male patient with Charcot Marie-Tooth disease who underwent a lower limb orthopedic surgery.

Introduction

Charcot-Marie-Tooth disease (CMTD) is a spectrum of various subtypes of inherited peripheral neuropathies. The disease affects approximately 1 in 2500 people and is caused by mutations in more than 30 genes which are necessary for myelin structure, maintenance, and formation. Most patients have a “classical” CMTD phenotype characterized by onset in the first two decades of life, distal weakness, sensory loss, foot deformities, and absent ankle reflexes. Life expectancy is not shortened and the treatment of the disease is mainly supportive. Particularly, orthopedic procedures are often required to treat foot deformities by the time of adolescence.

Due to nerve-damaging nature of CMTD, anesthesiologists fear possible exacerbation of the disease by different classes of drugs that act on these nerves in regional anesthesia. Moreover, some concerns have been expressed regarding the use of muscle relaxants in these patients. Although the issue of increased risk of malignant hyperthermia (MH) has been raised in these patients, most patients received MH triggering agents without untoward effects. However, available information does not exclude a potential link.

One way of minimizing the risks of anesthesia in these patients is by using total intravenous anaesthesia (TIVA). This can be done by using dexmedetomidine, a potent highly selective and specific α2-adrenoceptor agonist that has both sedative and analgesic effects which has been shown to consistently reduce the requirements of other anesthetic drugs.

We present a case report of a 17 year old CMTD patient who underwent an uneventful general anesthesia for a lower limb orthopedic surgery with total intravenous anesthesia using propofol and dexmedetomidine combined with caudal block using bupivacaine mixed with dexmedetomidine without any complications.
Case presentation

A 17-year old male patient (height = 135 cm weight = 19kg) was admitted for an orthopedic surgery. He is a known case of CMTD for 13 years. The diagnosis was made clinically, and confirmed by nerve conduction study and genetic studies. His physical examination reveals high arched left foot, distal muscle wasting, knee and ankle jerks were absent and sensation was decreased just below the knees. In the last month he developed difficulty in walking and he could not walk without assistance. He was planned for a posterior tibial tendon transfer, planter fascia release, gastrocnemius release and first ray dorsiflexion osteotomy. Preoperatively, the patient was fasting for eight hours, his American Society of Anesthesiologists (ASA) classification was 2, and his cardio-respiratory assessment was normal with good air entry bilaterally.

On the day of the operation, Soda lime, filters and circuit were changed, the anesthetic machine was washed with Oxygen 10 liter/minute for 15 minutes to eliminate any residual gas. Anesthesia plan was TIV A and Caudal block.

The patient was admitted to the operating room, and his blood pressure: 92/50 mm Hg, Pulse rate of 98 beats/minute, O2 saturation of 95% on room air. Intravenous (IV) access was secured and pre-oxygenation was done. Intravenous dexmedetomidine (Precedex®; Hospira, Lake Forest, Illinois, USA) of 20 mcg was administered over 15 minutes then propofol (60 mg) was given over two minutes. Ventilation was assessed, and then cisatracurium 0.1 mg/kg was given. Intubation was successful with oral endotracheal tube (size 5.5) from the first attempt without difficulties and the patient was mechanically ventilated. Anesthesia was maintained with propofol 5-10 mg/kg/hr and dexmedetomidine 0.2-0.5 mcg/kg/hr. Patient was placed in left lateral position and caudal block was done with 16 ml bupivacaine 0.25% mixed with preservative-free dexmedetomidine (20 mcg). Surgery lasted 140 minutes, through which there was no hypotension or bradycardia, and no muscle relaxant or opioids boluses were needed intraoperatively. At the end of the operation, patient was extubated and transferred to the recovery room and observed for two hours with uneventful course. Patient required first analgesia 12 hour after the operation. During a follow-up inquiry three months after surgery, the patient did not report any worsening of the underlying disease.

Discussion

Sporadic reports on the anesthetic management of CMTD have appeared in the literature, yet the main problem is the lack of controlled studies in these patients to evaluate potential risks of anesthesia. Up to this day, there is still a debate about the proper anesthetic care for surgical procedures for CMTD patients. In general, anesthetic care was adjusted to fit the individual needs of each patient6-10.

Therefore, due to the lack of enough evidence to exclude the risks of anesthetic drugs, the best way to deal with these patients is by minimizing the use of anesthetic drugs that have potential risks in these patients even though some reviews state that their use was safe and without untoward effects4.

CMTD patients have a chronic denervation, often in all extremities11. Since denervation is a potent predisposing factor for potassium release after exposure to succinylcholine (SCH)12, it is cautioned to use SCH in these patients. Moreover, the response to non-depolarizing neuromuscular blocking drugs is variable in patients with CMTD and their effects may be prolonged13-15. In this context, we used a single dose of cisatracurium (0.1 mg/kg) to facilitate the intubation.

Association between MH and the use of inhalational anesthesia in CMTD remains unclear. Despite the fact that sevoflurane is able to trigger malignant hyperthermia in susceptible patients16, the review of 86 cases indicates that most patients received MH triggering agents without untoward effects4. Moreover, according to The Charcot-Marie-Tooth Disease North American database, nitrous oxide is considered in the moderate to significant risk group of drugs for CMTD patients17. For that, no inhalational agent was used and the anesthesia machine was flushed with oxygen for 15 minutes before the surgery in order to eliminate any gas residues.

Patients with an underlying peripheral neurological disorder may be more susceptible to
nerve injury with the use of regional techniques for anesthesia, and the presence of chronic underlying neural compromise, may theoretically, place these patients at increased risk of further neurological injury. In order to alleviate the effects of regional anesthetic drugs in our case, we combined dexmedetomidine (20 mcg) with bupivacaine (40 mg) in the caudal block. This combination was found to prolong the duration of analgesia and decrease the amount of anesthetic drugs needed.

Dexmedetomidine is known for its remarkable pharmacological properties including sedation, anxiolysis, and analgesia with the unique characteristic to cause no respiratory depression. In addition, it possesses sympatholytic and antinociceptive effects that allow hemodynamic stability during surgical stimulation. It has shown to consistently reduce opioids, propofol, and benzodiazepines requirements.

CMTD has been reported to cause cardiac dysrhythmias and conduction disturbances, and is associated with increased incidence of mitral valve prolapse. Although bradycardia and hypotension are considered to be the most prominent adverse effects of α2-adrenoreceptor agonists, these side effects appear to be less pronounced when dexmedetomidine is given slowly over 15 minutes.

CMTD patients may have an increased sensitivity to thiopental, and the dose required is strongly related to the severity of the motor and sensory disturbance. However, propofol, as part of the total intravenous technique, is thought to be safe and effective. Therefore, we combined dexmedetomidine and propofol in TIVA to achieve the safest results in our case.

**Conclusion**

In conclusion, this case demonstrates the safety and effectiveness of the combined use of caudal dexmedetomidine and bupivacaine with intravenous dexmedetomidine and propofol for the anesthetic management of a patient with CMTD.
References

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LETTER TO THE EDITOR

ARTERIAL CANNULATION: SIMPLE SWAYING MANEUVER MAY BE AN ANSWER TO COUNTER FAILURE/COMPLICATION RATES

DEEPAK GUPTA* AND HASSAN H. AMHAZ**

Arterial cannulation is a commonly performed procedure in patients requiring hemodynamic monitoring in the perioperative period. Although not an exceedingly complex procedure, there can be an increase in cannulation failure rates and complications if simple maneuvers are ignored. Firstly, the intima-media thickness of radial artery is approximately 0.3 mm while the inner luminal diameter of the radial artery is approximately 3 mm as measured by angiography at its ideal insertion point. This ideal insertion point is at least 10 mm proximal to the R-U line (the surface marking line drawn latero-medially across the radial-ulnar styloid processes) so that the bifurcation point of the radial artery can be avoided during cannulation. Secondly, while cannulating the radial artery, anesthesia care providers may use either the Seldinger or modified Seldinger technique. With the Seldinger technique, the radial artery is punctured with a needle; after successful puncture, a separate non-integrated guidewire is threaded into the artery through the needle; over this in-situ guidewire, the catheter is slid over into the artery after removal of the needle. In the modified Seldinger technique (the most commonly used technique at our institution), the radial artery is punctured with a catheter-over-the-needle-over-the-integrated-wire assembly; successful needle puncturing the artery is appreciated by arterial blood flashback, then the guidewire is threaded into the artery through the needle, and subsequently once it is ensured that the guidewire has been threaded without any resistance into the arterial lumen, the catheter is slid over the needle-guidewire assembly.

Hereafter, the simple maneuver that is the focus of this letter is being explained based on the modified Seldinger technique for radial artery cannulation (with 4.45 cm long AK-04020, Integrated Seldinger technique Radial Artery Kit Version by ARROW® Arterial Products, Teleflex Incorporated, Morrisville, North Carolina, United States) [Fig. 1]. The described technique requires the swaying of the catheter-needle-guidewire assembly as a single unit and in that regards the sturdiness of the needle is apparently very essential to not allow the displacement of the assembly during the Swaying Maneuver.

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The basics underlying the Swaying Maneuver are simple. Per longitudinal section of an artery, it is always presumed that modified Seldinger technique cannulation can assume/follow just only one pathway after the arterial blood flashback has been visualized [Fig. 2]. However, when we change this two-dimensional viewpoint to a three-dimensional view, we realize that per transverse cross-sectional anatomy of the artery, the modified Seldinger technique can assume not one but three different pathways after the initial flashback. To better understand and explain these three different pathways, we need to divide the circular "walls" of the artery into (a) anterior "wall" meaning anterior-quarter of circumference that is nearest to the skin and is intentionally punctured for arterial cannulation, (b) posterior "wall" meaning posterior-quarter of circumference that is farthest away from the skin and is intentionally avoided unless the proceduralist intends to trans-fix the artery with transarterial through-and-through puncture of an artery, and (c) side "walls" meaning medial-lateral-quarters (two in number) of circumference that have never been discussed much but are the focus of this current letter.

As visualized in the transverse cross-section of an artery [Fig. 2], the needle-wire assembly can be in the center where the antero-posterior height/distance is maximum as it is equal to the inner luminal diameter; or it can be closer to side "walls" (either the medial one or the lateral one) wherein the antero-posterior height/distance will be less than the inner luminal diameter. This miniscule decrease in height/distance becomes significant when advancing the guidewire followed by the catheter as even the 3 mm inner luminal diameter in itself is very small distance at the center for manipulations of radial artery cannulation assembly. For this reason, when there is a arterial blood flashback, the catheter-needle-guidewire assembly has to be tilted from its original insertion angle (typically a 45° angle) at the time of arterial puncture to less than a 20° angle at the time of threading the guidewire into the arterial lumen so as to align the advancing guidewire along the longitudinal axis of the arterial lumen. Despite all this, the catheter tip may not have reached in the arterial lumen (stuck either within the arterial wall or outside the arterial wall) because of 0.3 mm intima-media thickness and at least 2 mm long bevel tip of 22-gauge-needle extending beyond the 20-gauge-
catheter tip [Fig. 3]. If the arterial puncture does not occur in the center (something that is beyond operator's control when using palpation method alone), the probability of reduced arterial blood flashback when tilting from an approximate 45° angle to less than a 20° degree angle increases as the anterio-posterior height/distance decreases as we move away from the center. Henceforth, the probability of the non-advancement of guidewire in spite of arterial blood flashback also increases; and herein if guidewire is forced further despite the resistance, the "stiff" guidewire can create false lumen within the arterial wall, can shear the catheter and can cause the non-functional/complicated arterial wall cannulation site.

The Swaying Maneuver is explained as follows: Firstly, it has to be ensured that the needle-bevel indicator on the catheter-needle-guidewire assembly indicates an anterior-facing bevel [Figure 1]. Then, once the assembly has punctured the arterial wall (as confirmed by arterial blood flashback) at a 45° angle to the skin, the angle is slowly reduced to an approximate angle of 20°. If the flashback is sustained during this reduction of angle, the needle is most likely aligned in the center and the guidewire will easily advance into the arterial lumen. If the flashback stops or slows while reducing the assembly’s angle, the needle bevel has likely apposed the anterior "wall" of the artery. This can be corrected by stopping any further reduction of the angle and rather a slight increase in the angle to a point to ensure the return of the sustained and good arterial blood flashback. At this point, if advancement of the guidewire is smooth, then the assembly is likely to be still relatively near the center of the artery and arterial cannulation should follow without difficulty. However, the scenario that’s commonly encountered is when there is a arterial blood flashback and yet the guidewire fails to advance despite performing the above mentioned maneuvers. In this case, the needle-guidewire assembly is in such close proximity to the medial or lateral "wall" of the artery that swaying of the entire assembly in the medio-lateral plane/direction must be done while maintaining the current arterial entry angle in the anterio-posterior plane. Whether this proximity is to the medial "wall" or lateral "wall" cannot be asserted unless the operator is confident that while palpating the artery, he/she had punctured the artery from the lateral side or the medial side of the palpable arterial pulsations. Irrespective of the operator's perceptions, if there is a reduction or cessation of the arterial blood flashback when swaying the assembly medially, then the assembly is likely closer to the medial "wall" of the artery and lateral redirection is required for re-negotiation of guidewire's advancement into the artery's center. Conversely, reduction or cessation of flashback when swayed laterally will indicate apposition to the lateral "wall" and hence will require medial redirection of the assembly. Once there is resumption of sustained and good arterial blood flashback, the guidewire should be advanced as by then, its advancement direction would have been re-negotiated centrally by the Swaying Maneuver allowing for successful arterial cannulation [Fig. 4].

In summary, when using the modified Seldinger technique for arterial cannulation, it is critical to understand the relationship among the catheter-needle-guidewire assembly, changes in angle, adequacy of flashback, and ease of guidewire advancement to help construct a mental image of the arterial catheter's position within the spatial coordinates of the artery being cannulated. Using the described Swaying Maneuver adds the final spatial clue that will allow for the central redirection and smooth advancement of the guidewire resulting in successful cannulation of the artery.
References


The Intercristal Line (ICL) is an imaginary line corresponding to the highest palpable level of the bilateral iliac crests. It is a common anatomical surface marker used by interventionalists to accurately guide needle access of lumbar cistern for cerebrospinal fluid (CSF) needed for diagnostic or therapeutic purposes. Recent evidence has questioned appropriateness of using ICL \(^1\) because of its variable anatomical proximity to conus medullaris (CM), the terminal lower end of spinal cord. However, the recent literature must NOT be misinterpreted as evidence to make the use of ICL completely redundant especially when palpation of ICL is required while blindly accessing lumbar cistern without fluoroscopy. In this regards, we would like to share our results about ICL and CM proximity (or lack of it) that were analyzed as an independent and exclusive sub-group analysis within the larger but non-overlapping data of our internal review board approved clinical investigation geared to identify the incidence of epidural lipomatosis among our pain clinic patients.

A retrospective sub-group analysis of 76 patients was performed among our pain clinic patients over a time-period of one year. In these patients, radiological proximity between ICL and CM was reviewed in the T1-weighted and T2-weighted magnetic resonance imaging (MRI) of lumbar spine available in our electronic medical record system. The results as elicited in Table 1 and Figure 1 show that in as many as 13% patients, CM can be prone to getting injured even when lumbar cistern access needle is introduced at lower than L1-L2 interspinous space; however, as a radiological marking based on the level of medial-most origin of iliacus muscle in the MRI, ICL appears to consistently cross at or above the L5 level. Consequently, when ICL is used as marker, up to 21% patients have only 1 or 2 interspinous spaces available cranially to safely access the lumbar cistern without the possibility of injuring CM. However, in difficult cases of lumbar cistern access, the interventionists can still injure CM when they steeply angulate and inappropriately re-direct their lumbar cistern access needles cranially despite the skin puncture site being in a safer lower level interspinous space with initial angle being appropriately perpendicular to the lumbar spine's skin.

There are few pearls highlighted by these results. Lumbar spine MRI based results can only give an overview of how spine behaves anatomically in supine position. The literature describes that palpated ICL, either with patients sitting upright during ultrasound \(^2\) or with patients in prone position during fluoroscopy \(^3\), is commonly cranial to radiological ICL per the confirming images of ultrasound \(^2\) or fluoroscopy \(^3\). However, it is not clear whether the proximity of palpated ICL to CM is due to erroneous palpation methods (as explained later in the text) or cranial movement of pelvis.
as a whole in relation to the spine when the patients are in sitting position or knee-chest position which are the two most common positions patients are in when being palpated for blind access to their lumbar cisterns. As displayed by Chakraverty et al, the radiological ICL being different (and usually caudal) than surface ICL potentially further decreases the number of available interspinous spaces for safely accessing lumbar cistern when interventionists are relying their decisions on inappropriately palpated surface ICL. Herein, we suggest a solution. To overcome the "belly fat tire" causing the surface ICL to be inappropriately palpated cranial to the radiological ICL (Figure 2), the best way is to locate ICL by step-up method of palpation (moving up in caudo-cranial direction). This is different from erroneous step-down method (moving down in cranio-caudal direction) that squeezes the "belly fat tire" between palpating hands and radiological ICL. The ideal hand positioning ensures that both index fingers of interventionists' pronated hands are parallel (and NOT at any angle) to the plane of ICL. Palpation by this method may commonly ensure that the surface ICL overlies on the radiological ICL and NOT cranial to it. This will further ensure that the number of good interspinous spaces are NOT decreased due to any erroneous method of ICL palpation. Subsequent to appropriate palpation of ICL, it is also important to ensure that the interventionists' thumbs are in the same plane as ICL and palpating index fingers so as to avoid the up-angulated thumbs palpatating (and identifying) interspinous space that can be inappropriately one level cranial to the intended interspinous space that is ideally located on the ICL plane or just caudal to the ICL plane (Figure 3).

In summary, all this micro-management for simple palpation of ICL and identifying appropriate interspinous space is to ensure that already restricted opportunity (in terms of number of available interspinous spaces) to safely access lumbar cistern does NOT become unsafe and/or inaccessible due to erroneously overlooked simple logistics of palpatating spine for lumbar cistern's access.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Spinous Process Level of Thoracolumbar Vertebrae</th>
<th>n (%) (Total 76 patients)</th>
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<tr>
<td>Conus Medullaris Accessible By Needle's Skin Puncture At Which Interspinous Level</td>
<td>T12-L1</td>
<td>23 (30%)</td>
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<tr>
<td></td>
<td>L1-L2</td>
<td>43 (57%)</td>
</tr>
<tr>
<td></td>
<td>L2-L3</td>
<td>9 (12%)</td>
</tr>
<tr>
<td></td>
<td>L3-L4</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Intercristal Line NOT Below This Level Based On Iliacus Muscle Medial-Most Origin</td>
<td>L4</td>
<td>11 (14%)</td>
</tr>
<tr>
<td></td>
<td>L4-5</td>
<td>34 (45%)</td>
</tr>
<tr>
<td></td>
<td>L5</td>
<td>30 (40%)</td>
</tr>
<tr>
<td></td>
<td>L5-S1</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Good Interspinous Spaces Available Cranial To ICL for Needle Access (Median=3; Mode=3)</td>
<td>1</td>
<td>2 (3%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>14 (18%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>40 (53%)</td>
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<tr>
<td></td>
<td>4</td>
<td>20 (26%)</td>
</tr>
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</table>

Table 1

**Intercristal Line (ICL) And Conus Medullaris (CM) Proximity**

Fig. 1

Graphical Presentation of Intercristal Line and Conus Medullaris Proximity
Fig. 2

Step-Up vs. Step-Down Method for Palpation of Intercristal Line

Fig. 3

Appropriate Alignment of Palpating Thumbs and Fingers in Relation to Intercristal Line
References


GUIDELINES FOR AUTHORS

The Middle East of Anesthesiology publishes original work in the fields of anesthesiology, intensive care, pain, and emergency medicine. This includes clinical or laboratory investigations, review articles, case reports and letters to the Editor.

Submission of manuscripts:

The Middle East Journal of Anesthesiology accepts electronic submission of manuscripts as an e-mail attachment only.

Manuscripts must be submitted via email attachment to:

Editor-In-Chief,
Department of Anesthesiology,
American University of Beirut Medical Center
Beirut, Lebanon
E-mail: meja@aub.edu.lb

Human Subjects

Manuscripts describing investigations performed in humans must state that the study was approved by the appropriate Institutional Review Board and written informed consent was obtained from all patients or parents of minors.

Language:

Articles are published in English.

Manuscript Preparation

Manuscript format required:

- Double-spaced lines
- Wide margins (1.5 inches or 3.8 cm)
- Page numbers start on title page
- Word count should reflect text only (excluding abstract, references, figures and tables).

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<td>Editorial</td>
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<td>Abstract</td>
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<td>Review article</td>
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<td>Case Reports</td>
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Clinical or laboratory investigations:

The following structured format is required:

1. Cover Letter 7. Discussion
2. Title page 8. Acknowledgements
3. Abstract 9. References
4. Introduction 10. Tables
5. Methods 11. Figures
6. Results

1. Cover Letter

Manuscripts must be accompanied by a cover letter, signed by all authors and stating that:
- All authors have contributed intellectually to the manuscript and the manuscript has been read and approved by all the authors.
- The manuscript has not been published, simultaneously submitted or accepted for publication elsewhere.

2. Title Page

Starts at page 1 and includes:
- A concise and informative title (preferably less than 15 words). Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific.
- Authors listing: first name, middle initial and last name with a superscript denoting the academic degrees as footprints.
- The name of the department(s) and institutions(s) to which the work should be attributed.
- The name, address, telephone, fax numbers and e-mail address of the corresponding author.
- Disclose sources of financial support (grants, equipment, drug etc…).
- Conflict of interest: disclosure of any financial relationships between authors and commercial interests with a vested interest in the outcome of the study.
- A running head, around 40 characters.
- Word count of the text only (excluding abstract, acknowledgements, figure legends and references).

3. Abstract

Abstract should follow the title page. It should be structured with background, methods, results and conclusion.

M.E.J. ANESTH 23 (5), 2016
It should state, the specific purpose of the research or hypotheses tested by the study, basic procedures, main findings and principal conclusions.

Provide separate word count for the abstract.

4. Introduction

Provide the nature of the problem and its significance. State the specific purpose or research objectives or hypothesis tested. Provide only directly pertinent references and do not include data or conclusions from the work being reported.

5. Methods

A. Selection and description of participants:
   - Describe selection of participants (including controls) clearly, including eligibility and exclusion criteria.

B. Technical Information:
   - Identify the methods, apparatus (give the manufacturer’s name and address in parentheses), and procedure in sufficient detail to allow others to reproduce the results. Give references to established methods. Provide references and brief descriptions for methods that have been published. Identify precisely all drugs and chemicals used, including generic names(s), dose(s) and routes(s) of administration.

C. Statistics-describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. Define statistical terms, abbreviations and most symbols. Specify the computer software used. Provide a power analysis for the study.

6. Results

Present your results in logical sequence in the text, tables and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text: emphasize or summarize only the most important observations. Extra or supplementary materials and technical details can be placed in an appendix.

7. Discussion

Emphasize the new and important findings of the study and the conclusions that may be drawn.

Do not repeat in details data or other information given in the Introduction or the Results sections. For experimental studies, it is useful to begin the discussion by summarizing briefly the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies. State the limitations of the study, and explore the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study, but avoid unjustified statements and conclusions not adequately supported by the data.

8. Acknowledgements

They should be brief. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgments.

9. References

- References should be indicated by Arabic numerals in the text in the form of superscript and listed at the end of the paper in the order of their appearance. Please be accurate, giving the names of all authors and initials, the exact title, the correct abbreviation of the journal, year of publication, volume number and page numbers.

- The titles of journals should be abbreviated according to the style used in the list of Journals Indexed for MEDLINE.

Example: (1) from a journal (2) from a book.


10. Tables

Tables capture information concisely and display it efficiently: They also provide information at any desired level of details and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

   - Type or print each table with double spacing on a separate sheet of paper.
   - Number tables consecutively in the order of their first citation in the text.
   - Supply a brief title for each.
   - Place explanatory matter in footnotes, not in the heading.
   - Explain all nonstandard abbreviations in footnotes.
   - Identify statistical measures of variations, such as standard deviation and standard error of the mean.

11. Figures

- Figures should be submitted in JPEG or TIFF format with a minimum of 150 DPI in resolution.
- Colored data if requested by author is chargeable.
- If a figure has been published previously, acknowledge the original source and submit written permission from the copyrights holder to produce the figure.

Abbreviations and symbols:

   - Use only standard abbreviations.
   - Avoid abbreviations in the title of the manuscript.
   - The spelled-out abbreviations followed by the abbreviation in parenthesis should be used in first mention.