Opioid Free Versus Opioid Based Anesthesia in Major Spine Surgery: A Prospective, Randomized, Controlled Clinical Trial

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Research Article

Keywords: Spine, opioid-free anesthesia, Dexmedetomidine, Lidocaine, Remifentanil, ketamine, morphine

Posted Date: March 16th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2515135/v1

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Minerva Anestesiologica on June 1st, 2024. See the published version at https://doi.org/10.23736/S0375-9393.24.17962-X.
Abstract

Background: The aim of this study is to compare the intraoperative opioid free anesthesia approach to the conventional opioid based anesthesia in patients undergoing multilevel spinal fusion surgery, and its impact on postoperative pain, opioid consumption, and related side effects.

Methods: Forty-eight patients undergoing elective major spine surgery were randomly allocated to two groups. The Opioid-Free Anesthesia (OFA) group received dexmedetomidine 0.5mcg/kg/hr and lidocaine 1mg/kg/hr as continuous intravenous (IV) infusion for 10 minutes before anesthesia induction, followed by dexmedetomidine 0.3 mcg/kg/hr and lidocaine 1.5mg/kg/hr as continuous IV infusion intraoperatively. The Opioid-Based Anesthesia (OBA) group received fentanyl 2mcg/kg during anesthesia induction and remifentanil 0.2-0.3 mcg/kg/min continuous IV infusion intraoperatively. All patients received ketamine 0.15mg/kg, propofol 2 mg/kg and rocuronium 0.6 mg/kg for anesthesia induction and ketamine 0.15 mg/kg/hr with sevoflurane for anesthesia maintenance. All patients received a Patient Controlled Analgesia (PCA) device set to deliver IV morphine ready for use directly after discharge from the Post Anesthesia Care Unit (PACU) for 48 hours after surgery. Postoperative pain was measured using Verbal Analogue Scale (VAS). Opioid side effects were documented when present.

Results: The OFA group required less morphine consumption in the first 24 hours post-surgery (17.28 ± 12.25 mg versus 27.96 ± 19.75 mg, p < 0.05). The incidence of nausea and vomiting was significantly lower in the OFA group. There was no significant difference in the hemodynamic changes intraoperatively among the two groups. However, more patients in the OFA group required antihypertensive medications compared to patients in the OBA group (p< 0.05). In the PACU, OFA patients had a significantly longer stay than OBA patients (114.1± 49.33 min versus 89.96 ± 30.71 min, p<0.05), yet there was no significant difference in the morphine consumption.

Conclusion: OFA can be an alternative to OBA in patients undergoing multilevel spine fusion surgery. OFA use resulted in reduced need for analgesics for the first 24 hours and less postoperative nausea and vomiting.

Trial registration: The study was conducted after receiving approval from local Institutional Review Board, Lebanese American University, Institutional Review Board (LAU IRB) (LAUMCRH.HB1.11/01/2018): and was registered with ClinicalTrials.gov (registration number: NCT03417193) and posted on 31/01/2018.

Background

Spinal fusion surgery can result in severe postoperative pain making pain management a primary concern given that persistent pain leads to negative impact on physical, social, and emotional health. Effective perioperative analgesia is not only a humane necessity but is important to prevent short-term and long-term complications. Opioids remain the primary systemic pharmacotherapy for intraoperative and postoperative analgesia, particularly for moderate to severe pain. However, perioperative opioid use
may be associated with serious adverse effects and significant morbidity. Opioids’ undesirable side effects include nausea/vomiting, constipation/ileus, pruritus, altered mental status, and respiratory depression, which is the most dangerous of these effects. In addition, excessive postoperative opioid prescribing contributes to the ongoing opioid crisis. Furthermore, the liberal use of intraoperative opioids might result in increased postoperative opioid consumption. Some studies suggest switching to opioid-free anesthesia (OFA) which is largely based on the avoidance of opioid related adverse events. OFA is defined as a technique in which no intraoperative opioid is administered via any route, namely systemic, neuraxial, or by tissue infiltration. Analgesia can be reached with a multimodal administration of non-opioid agents such as N-methyl-d-aspartate antagonists (NMDA), local anesthetics, and α2 agonists.

Although the effectiveness of OFA technique was studied in many surgeries such as bariatric surgery and laparoscopic cholecystectomy, yet no randomized clinical trial was performed on patients undergoing multilevel posterior spinal fusion surgery using this technique. On the other hand, OFA was proposed to be especially valuable in patients with high risk of opioid-related complications, including those with chronic pain conditions and opioid misuse disorder. Patients undergoing major spine surgery usually experience chronic back pain and are on chronic use of analgesics, as such, deserve special attention, and a wider adoption of best perioperative and intraoperative pain management strategies is required.

The aim of this prospective, randomized, controlled study is to compare the effects of OFA and the opioid-based anesthesia (OBA) techniques, on analgesic requirements in the first 48 hours post-surgery, in patients undergoing multi-level spine fusion surgery (primary outcome). The secondary outcomes include intraoperative hemodynamic stability, duration of Post Anesthesia Care Unit (PACU) stay, postoperative pain scores, total post-operative opioid consumption up to 48 hours and opioid-related side effects.

**Methods**

**Study Design**

This is a prospective, single-blind, randomized, single-center study that was performed at the Lebanese American University Medical Center, Beirut, Lebanon. The study was approved by the local Institutional Review Board (LAUMCRH.HB1. 11/01/2018) and was registered with ClinicalTrials.gov (registration number: NCT03417193) and posted on 31/01/2018.

; principal investigator: H Barakat. Written informed consent was obtained from all participating patients before inclusion in the study. After obtaining informed written consent for participation in the study, 48 adult patients 18-80 years of age (American Society of Anesthesiologist (ASA) class I-III) of both genders undergoing at least two-level, elective posterior fusion spine surgery under general anesthesia were enrolled in this study between February 2018 and September 2020. All patients were assessed
preoperatively, and participation in the study as well as existing alternatives were discussed. Patients who were allergic to the study drugs, or patients with renal, hepatic and/or cardiac insufficiency, alcohol or drug abuse, psychiatric disease, and inability to comprehend pain assessment or to use a Patient Controlled Analgesia (PCA) device were excluded from the study.

Patients were randomized in a 1:1 ratio to either the OFA group or the OBA group according to a computerized random-number generator that was used to formulate an allocation schedule. The randomization scheme was generated using the website randomization.com. On the morning of surgery, participants were assigned an identification number which was identical to the code of the protocol that they received intraoperatively.

Treatment assignments were concealed from patients. The anesthesia resident in charge of the patient performed the allocation according to the randomization schedule on the day of surgery. The anesthesia team (anesthesiologist, anesthesia resident and anesthesia nurse) prepared and administered the medications to the patient during anesthesia and collected the data during surgery. This team was not involved in the post-operative assessment at any time.

A PACU nurse, not part of the research team and who was blinded to the type of intervention received by the participant, recorded the pain scores, opioid consumption, and side effects after arrival to the PACU (0 hour) and every 10 minutes until discharge. An anesthesia resident, unaware of the treatment allocation, recorded the pain scores and opioid consumption from the time when the patient was transferred to the surgical ward till 48 hours post-surgery. Any side effect encountered during each visit was also documented.

**Intraoperative and Postoperative Care**

Upon entry to the operating room, all patients received standard ASA monitoring including a 5-lead electrocardiogram (ECG) for continuous cardiac monitoring including heart rate (HR), non-invasive blood pressure (BP) monitoring, pulse oximeter for oxygen saturation monitoring and capnography. A 20-gauge venous cannula was inserted. All patients underwent general anesthesia, and the radial artery was cannulated for invasive intraoperative arterial BP monitoring just after the induction of anesthesia. Intraoperatively, HR and BP were monitored and documented at baseline then every 10 minutes till the end of surgery and upon arrival to the PACU.

In the OFA group, patients received dexmedetomidine 0.5 mcg/kg/hr and lidocaine 1 mg/kg/hr as continuous intravenous (IV) infusion over 10 minutes prior to induction of anesthesia. Anesthesia was induced using Propofol 2 mg/kg, rocuronium 0.6 mg/kg and ketamine 0.15 mg/kg. After tracheal intubation, anesthesia was maintained with dexmedetomidine 0.3 mcg/kg/hr, lidocaine 1.5 mg/kg/hr, ketamine 0.15 mg/kg/hr infusion and inhaled sevoflurane between 0.5-2%.

In the OBA group, anesthesia was induced using Propofol 2 mg/kg, fentanyl 2 mcg/kg, rocuronium 0.6 mg/kg and ketamine 0.15 mg/kg. After tracheal intubation, remifentanil IV infusion was initiated with a
dose range of 0.2-0.3 mcg/kg/min depending on the patients’ hemodynamic status. Anesthesia was also maintained using ketamine infusion 0.15 mg/kg/hr and inhaled sevoflurane between 0.5-2%.

Atropine or glycopyrolate were used to keep a HR above 45 beats/min. On the other hand, phenylephrine, ephedrine, or nicardipine and labetolol were used to prevent hypotension, defined as mean arterial pressure (MAP) lower than 65 mmHg, or hypertension defined as MAP higher than 90 mmHg.

The infusion of dexmedetomidine was stopped at the beginning of skin closure whereas the infusion of remifentanil was stopped when last suture was done. Nefopam 20mg, a non-opioid, non-steroidal, centrally acting analgesic drug, and Paracetamol 1g were administered intravenously 30 minutes before the end of surgery. Residual neuromuscular block was antagonized with IV neostigmine 0.04mg/kg and glycopyrrolate 0.01mg/kg. Sevoflurane was discontinued after the last skin suture. After extubation, patients were transferred to the PACU. HR and BP were documented at baseline, after induction of anesthesia, skin incision, then every 10 min till the end of surgery, during extubation and just before transfer to PACU. Episodes of bradycardia, hypotension and hypertension were recorded. The total duration of anesthesia and surgery were recorded.

In the PACU, morphine was titrated every 5 min by 2 mg increments when verbal analogue scale (VAS) score was more than 4. Patients were discharged to the surgical ward after they satisfied the PACU discharge criteria. The discharge criteria included level of consciousness, respiratory stability, oxygen saturation status, hemodynamic stability, post-operative pain (VAS score) and post-operative nausea and vomiting.

At discharge from PACU, all patients received a PCA device, set to deliver morphine sulfate at a concentration of 1mg/ml, with a demand dose of 1mg and lockout interval of 6 minutes. Patients also received Paracetamol 1g IV every 6 hours as part of the postoperative pain control regimen.

Opioid consumption, pain scores and side effects were recorded at the time of discharge from PACU, and subsequently at 1, 2, 4, 6, 12, 18 and 24 hours, then every 6 hours till 48 hours post-surgery.

**Primary and secondary outcomes**

The primary outcome was the opioid consumption for the first 48-hour post-surgery. Secondary outcomes were intraoperative cardiac events during surgery (determined through the need of vasopressors, vagolytics and antihypertensive medications), time to extubation, time to reach PACU discharge criteria, and episodes of postoperative pain (defined as any episode with VAS score equal to or greater than 4) within 48 h after surgery.

In addition, post-operative opioid related side effects including pruritus, nausea and vomiting, respiratory depression, and sedation were considered as secondary outcomes. Time points for post-operative opioid related side effects, including nausea and vomiting, were performed according to the schedule set for postoperative assessment.
Statistical Analysis

The sample size requirement was based on a clinically significant difference of 17 mg of morphine between the 2 groups and the standard deviation of 20.\textsuperscript{10} At an alpha risk of 0.05, 44 patients (22 in each group) were sufficient to provide 80% power. To allow for the potential unevaluable patients, and an allocation ratio of 1, 48 participants were enrolled.

The statistical analysis was conducted using the SPSS v.28 statistical program. Demographics are summarized using the mean +/- standard deviation for continuous measures and as frequencies for categorical variables.

The Shapiro test was used to test for normality, the independent t-test was used in case of normal distribution, while the Mann Whitney U test was used in case of non-normality. The chi-squared test of independence and Fisher exact test were used to assess the relationship between categorical variables. A p-value < 0.05 was considered statistically significant.

Results

Of the 86 patients assessed for eligibility, 59 patients underwent randomization, and 48 patients were included in our data analysis (25 patients in the OFA group and 23 patients in the OBA group) [Figure.1]. Although, most cases were females, there was no statistical difference between the two groups according to demographic data of age, gender, weight, height, ASA score and number of levels operated on (p>0.05) [Table.1]. There was no significant difference in baseline MAP (p=0.092) and HR (p=0.391) [Table.1].
Table 1: Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>OFA</th>
<th>OBA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64.32 ± 10.61</td>
<td>65.43 ± 11.89</td>
<td>0.508</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>9/16</td>
<td>7/16</td>
<td>0.683</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>82.12 ± 17.41</td>
<td>77.33 ± 15.24</td>
<td>0.317</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.2 ± 10.19</td>
<td>163.61 ± 9.87</td>
<td>0.179</td>
</tr>
<tr>
<td>ASA Score</td>
<td></td>
<td></td>
<td>0.574</td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>17</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Levels</td>
<td>4.32 ± 1.75</td>
<td>3.78 ± 1.28</td>
<td>0.313</td>
</tr>
<tr>
<td>Baseline MAP (mm/Hg)</td>
<td>97.01 ± 13.14</td>
<td>102.91 ± 10.3</td>
<td>0.092</td>
</tr>
<tr>
<td>Baseline HR</td>
<td>76.76 ± 11.95</td>
<td>79.57 ± 10.36</td>
<td>0.391</td>
</tr>
</tbody>
</table>

Intraoperatively, there was no significant difference in MAP at induction (p= 0.918), 10 min after induction (p= 0.288), incision (p= 0.223), 10 min from incision (p= 0.563), 60 min from incision (p=0.321), end of surgery (p=0.845). and on emergence (p=0.088) between both groups [Table.2]. There was no significant difference in HR between both group at induction (p=0.996), 10 min after induction (p= 0.338), incision (p=0.067), 10 min from incision (p= 0.052), 60 min from incision (p= 0.502), end of surgery (p=0.982) and on emergence (p=0.315) [Table.2].
Table.2 Intraoperative Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>OFA</th>
<th>OBA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>92.25 ± 12.17</td>
<td>94.01 ± 17.95</td>
<td>0.918</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>74.20 ± 10.10</td>
<td>74.22 ± 11.50</td>
<td>0.996</td>
</tr>
<tr>
<td><strong>10 min from Induction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>85.17 ± 17.47</td>
<td>79.13 ± 17.84</td>
<td>0.288</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>74.88 ± 12.70</td>
<td>71.43 ± 11.88</td>
<td>0.338</td>
</tr>
<tr>
<td><strong>Incision</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>73.39 ± 14.66</td>
<td>69.01 ± 12.83</td>
<td>0.223</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>68.28 ± 10.31</td>
<td>64.74 ± 6.27</td>
<td>0.067</td>
</tr>
<tr>
<td><strong>10 min from Incision</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>69.77 ± 12.17</td>
<td>71.70 ± 10.56</td>
<td>0.563</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>71.32 ± 18.42</td>
<td>62.04 ± 10.96</td>
<td>0.052</td>
</tr>
<tr>
<td><strong>60 min from Incision</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>68.48 ± 7.08</td>
<td>71 ± 10.18</td>
<td>0.321</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>63.64 ± 8.47</td>
<td>61.96 ± 8.74</td>
<td>0.502</td>
</tr>
<tr>
<td><strong>End of Surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>77.01 ± 11.49</td>
<td>70.33 ± 16</td>
<td>0.845</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70.08 ± 10.73</td>
<td>70 ± 13.15</td>
<td>0.982</td>
</tr>
<tr>
<td><strong>Emergence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>86.61 ± 11.45</td>
<td>93.12 ± 14.55</td>
<td>0.088</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>78.84 ± 13.39</td>
<td>82.96 ± 14.66</td>
<td>0.315</td>
</tr>
</tbody>
</table>

OFA patients received more intraoperative antihypertensives compared to the OBA patients (p=0.004) and there was no significant difference between intraoperative vasopressor use (p=0.725) [Table.3]. The duration from end of surgery till extubation was not significant (p=0.884) [Table.3].
Table 3: Intraoperative Data

<table>
<thead>
<tr>
<th></th>
<th>OFA</th>
<th>OBA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction to Incision (min)</td>
<td>48.48 ± 13.94</td>
<td>49.7 ± 11.51</td>
<td>0.745</td>
</tr>
<tr>
<td>Surgery (min)</td>
<td>191.96 ± 47.98</td>
<td>161.65 ± 40.11</td>
<td>0.051</td>
</tr>
<tr>
<td>Anesthesia (min)</td>
<td>258.64 ± 55.31</td>
<td>229.39 ± 36.54</td>
<td>0.077</td>
</tr>
<tr>
<td>End of Surgery till Extubation (min)</td>
<td>18.2 ± 8.72</td>
<td>18.04 ± 8.06</td>
<td>0.884</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative Antihypertensive (dose)</td>
<td>1.64 ± 2.34</td>
<td>0.35 ± 0.88</td>
<td>0.004*</td>
</tr>
<tr>
<td>Intraoperative Vasopressors (dose)</td>
<td>9.8 ± 8.95</td>
<td>9.02 ± 9.02</td>
<td>0.725</td>
</tr>
</tbody>
</table>

*Significance (p-value<0.05)

In the PACU, the OFA patients required a significantly longer duration of stay (p=0.036). There was no significant difference in the total morphine consumption (p=0.134), and VAS upon discharge (p=0.101) [Table 4].

Table 4: PACU

<table>
<thead>
<tr>
<th></th>
<th>OFA</th>
<th>OBA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine Consumption (mg)</td>
<td>5.08 ± 4.86</td>
<td>6.57 ± 4.12</td>
<td>0.134</td>
</tr>
<tr>
<td>Duration of Stay (min)</td>
<td>114.1 ± 49.33</td>
<td>89.96 ± 30.71</td>
<td>0.036*</td>
</tr>
<tr>
<td>VAS upon Discharge</td>
<td>1 ± 1.16</td>
<td>1.52 ± 0.99</td>
<td>0.101</td>
</tr>
</tbody>
</table>

*Significance (p-value<0.05)

There was no significant difference in cumulative morphine consumption at 1 hour, 6 hours, and 12 hours after surgery (p-value > 0.05) [Table 5], yet the cumulative 0 to 24h postoperative morphine consumption was significantly less in the OFA group (p=0.031). There was no significant difference in the cumulative postoperative morphine consumption between both groups from 24 to 48 hours postsurgery (p=0.627), nor the cumulative consumption at 48 hours (p=0.103).
Table.5 Postoperative Morphine Consumption (mg)

<table>
<thead>
<tr>
<th>Postoperative Time</th>
<th>OFA</th>
<th>OBA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour</td>
<td>1.68 ± 1.91</td>
<td>2.04 ± 2.12</td>
<td>0.530</td>
</tr>
<tr>
<td>6 hours</td>
<td>7.08 ± 4.99</td>
<td>12.87 ± 11.91</td>
<td>0.063</td>
</tr>
<tr>
<td>12 hours</td>
<td>11.04 ± 8.96</td>
<td>17.13 ± 13.83</td>
<td>0.057</td>
</tr>
<tr>
<td>24 hours</td>
<td>17.28 ± 12.25</td>
<td>27.96 ± 19.75</td>
<td>0.031*</td>
</tr>
<tr>
<td>48 hours</td>
<td>34 ± 30.43</td>
<td>43.57 ± 25.67</td>
<td>0.103</td>
</tr>
<tr>
<td>24-48 hours</td>
<td>16.64 ± 20.44</td>
<td>16.09 ± 13.08</td>
<td>0.627</td>
</tr>
</tbody>
</table>

*Significance (p-value<0.05)

There was no significant difference in VAS scores between both groups, at 24 hours and 48 hours postoperatively (p=0.095 and p=0.315, respectively) [Table 6].

Table.6 Postoperative VAS Score

<table>
<thead>
<tr>
<th>Postoperative Time</th>
<th>OFA</th>
<th>OBA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>1.88 ± 1.01</td>
<td>2.48 ± 1.12</td>
<td>0.095</td>
</tr>
<tr>
<td>48 hours</td>
<td>1.04 ± 0.94</td>
<td>1.3 ± 0.93</td>
<td>0.315</td>
</tr>
</tbody>
</table>

Documented postoperative side effects included nausea alone or both nausea and vomiting. There was a significant difference between both groups (p=0.02939) [Table 7]. 26.09% of patients in the OBA group experienced nausea alone and 26.09% experienced both nausea and vomiting, while most patients in the OFA group didn't experience any side effects (84%) [Table.7].

Table.7 Opioid Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>OFA (n=25)</th>
<th>OBA (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>21 (84%)</td>
<td>11 (47.82%)</td>
<td></td>
</tr>
<tr>
<td>Only nausea</td>
<td>2 (8%)</td>
<td>6 (26.09%)</td>
<td>0.02939*</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2 (8%)</td>
<td>6 (26.09%)</td>
<td></td>
</tr>
</tbody>
</table>

*Significance (p-value<0.05)

Discussion

In this prospective, randomized open-label study, opioid-free balanced anesthesia with dexmedetomidine, lidocaine and ketamine resulted in a decreased postoperative morphine consumption.
in the first 24 hours when compared with balanced anesthesia with remifentanil and ketamine in patients undergoing major spine surgery. Patients in the OFA group did not experience more intraoperative episodes of bradycardia and hypotension requiring rescue medications. They also experienced less postoperative nausea and vomiting but prolonged PACU duration.

There is evidence that opioid-free anesthesia, when compared with opioid-based anesthesia, does not present inferior results regarding pain scores or opioid consumption in the postoperative period.\textsuperscript{17} Also, OFA has been shown to decrease postoperative opioid consumption in bariatric surgery,\textsuperscript{18} gynecological procedures,\textsuperscript{19} spine surgery,\textsuperscript{11} and more recently in cardiac surgery.\textsuperscript{20} In our study, there was no significant difference in the opioid consumption between the two groups in the PACU, however the OFA patients received significantly less morphine than the OBA patients in the first 24 hours after surgery, although there was no significant difference in morphine consumption between both groups at 48 hours from surgery. Similar results for the morphine consumption during the first 24 hours were reported by Grape et al.\textsuperscript{21} The mechanism by which dexmedetomidine provides this 24 hours long term analgesic effect, and possibly, longer pro-analgesic effect is still not established.\textsuperscript{22}

In our study, the opioid-free balanced anesthesia regimen included dexmedetomidine, lidocaine and ketamine, to benefit from each of these drug individual mechanisms of action for amelioration of intraoperative and postoperative pain.

Dexmedetomidine is an alpha-2 agonist that has hypnotic, sedative, and analgesic properties. Boojaraaj et al, reported that the use of IV dexmedetomidine decreased the total amount of intraoperative fentanyl and propofol required for maintenance of anesthesia during elective spine surgeries.\textsuperscript{23} The main adverse event seen with dexmedetomidine administration is the hemodynamic instability, namely bradycardia, hypotension, and hypertension.\textsuperscript{24} These episodes of hemodynamic disturbances have been associated with the use of high loading dose or fast initial infusion rates.\textsuperscript{25} The prevalence of bradycardia was reported to be significantly lower with a loading dexmedetomidine dose of 0.5 mcg/kg than with loading doses of 1 or 0.75 mcg/kg.\textsuperscript{26,27} In our study, a loading dose of dexmedetomidine 0.5 mcg/kg infused over 10 minutes and followed by a maintenance dose of 0.3 mcg/kg/hr was used.

Lidocaine is an amide local anesthetic with many reported benefits such as reduction in pain, opioid requirement, ileus duration, nausea and length of hospital stay.\textsuperscript{28} A meta-analysis and systematic review focusing on the effect of perioperative IV lidocaine in spine surgery showed that perioperative IV lidocaine attenuated the pain intensity up to 48 hours after the surgery and reduced opioid consumption.\textsuperscript{29} In addition, despite the well-described safety profile in numerous clinical trials, it must be reiterated that systemic lidocaine has a very narrow therapeutic index given that central nervous system (CNS) toxicity occurs (> 5 mcg/ml) slightly above the therapeutic plasma level (2.5–3.5 mcg/ml).\textsuperscript{30} According to an international consensus statement on efficacy and safety for IV lidocaine use, a loading dose of no more than 1.5mg/kg, given as an infusion over 10 min, is recommended and an infusion of no
more than 1.5mg/kg/h, for no longer than 24 h, is recommended, subject to review and reassessment.\textsuperscript{31} In our study, these doses were respected.

Ketamine was used in all patients in our study, including patients who received remifentanil. Ketamine is a widely used NMDA receptor antagonist.\textsuperscript{32} Ketamine reduces postoperative analgesic consumption and pain intensity according to a Cochrane review.\textsuperscript{33} Patients who benefited the most were those undergoing surgery in which the postoperative pain was expected to be severe, such as spine surgery.\textsuperscript{34} In addition, ketamine might also influence the opioid-induced hyperalgesia (OIH) developed with the use of remifentanil. In fact, there is evidence that glutamate release and NMDA receptors activation may be important key players in the development of OIH.\textsuperscript{35} A meta-analysis by Wu \textit{et al}, showed that NMDA receptor antagonists (ketamine and magnesium) can prevent the increase of analgesic consumption and pain intensity induced by remifentanil, improving postoperative patient satisfaction.\textsuperscript{36}

One of the compelling reasons to avoid opioids in surgical patients is their significant side effects such as respiratory depression and/or obstruction, nausea, vomiting, constipation and ileus, urinary retention, sedation, and cognitive dysfunction.\textsuperscript{9} Specific population of surgical patients may be even more likely to benefit from OFA, such as patients suffering from chronic pain\textsuperscript{37,38} and who are on chronic analgesics use, like our patients.\textsuperscript{16} Benefits in this category of patients are suggested by the association between opioid exposure and OIH. OIH is a paradoxical increase in pain sensitivity and decrease in pain tolerance following the administration of opioids.\textsuperscript{39} Intraoperative remifentanil infusion was particularly associated as a risk factor for its development.\textsuperscript{35} Accordingly, OFA was proposed as a strategy to prevent OIH after multiple surgical subtypes, including spinal fusion.\textsuperscript{40} However, the safety of the OFA technique is still not well established. A trial recently published by Beloeil \textit{et al}, where a balanced OFA with dexmedetomidine was compared with remifentanil, resulted in greater incidence of serious adverse events, especially hypoxemia and bradycardia, leading to early termination of the trial.\textsuperscript{41} A meta-analysis, published by Salome \textit{et al}, suggested that caution is necessary in the development of adequate OFA regimen, as more data is needed to establish OFA safe use.\textsuperscript{42} Increased opioid use was linked to increased wound complications after cervical spine surgery\textsuperscript{43} and delayed healing in rabbit spinal fusion model.\textsuperscript{44}

Our results showed no difference in intraoperative BP and HR between both groups. Previous studies suggested that the intraoperative hemodynamic stability and the antinociception traditionally obtained by opioids could be reached with a multimodal administration of nonopioid agents such as NMDA antagonists, local anesthetics, and \(\alpha\)-2 agonists.\textsuperscript{41}

OFA patients required more antihypertensive administration than OBA patients. A similar finding was reported in a study by Bakan \textit{et al}, where 28\% of patients in the dexmedetomidine group required nitroglycerin to treat intraoperative hypertension, mostly at the beginning.\textsuperscript{14} A 0.3 mcg/kg/hr maintenance dose of dexmedetomidine was used in both studies which could explain the similarity in results.
Studies reported more ephedrine use in patients receiving remifentanil than in patients receiving dexmedetomidine due to the higher hypotension risk associated with remifentanil infusion. However, in our study, there was no significant difference in the dose of vasopressors used. The addition of low dose ketamine to remifentanil in the OBA group could explain our results. Remifentanil is an ultra-short-acting phenylpiperidine opioid analgesic that has high lipid solubility, and hence, a rapid onset of effect. It is rapidly metabolized by non-specific blood and tissue esterases, which results in a rapid recovery. Studies reported bradycardia and hypotension to be likely caused by a centrally mediated increase in vagal nerve activity. Subanesthetic ketamine dose was shown to increase both BP and HR without causing hypertensive events. Mustafa et al, reported that the addition of low dose ketamine infusion to remifentanil infusion in adolescent patients who underwent posterior spinal fusion surgery did not decrease HR and MAP values below the preoperative values. Hasanein et al, showed that the co-administration of low dose ketamine and remifentanil by continuous infusion provides more hemodynamic stability in morbidly obese patients undergoing laparoscopic gastric bypass surgery compared to remifentanil and saline continuous infusion.

There was no difference in extubation time between patients of both groups. Several studies reported similar findings. PACU duration stay was longer in the OFA patients compared to the OBA patients. There is conflicting data concerning the effect of OFA on the length of PACU stay. A review article on the effect of OFA on perioperative period reported a prolonged PACU length of stay in the opioid free group. Patients undergoing thyroidectomy who received intraoperative dexmedetomidine had a longer PACU stay time compared to those who received intraoperative remifentanil. These results were similar to our findings. However, Hwang et al, did not find a statistical significance in PACU duration stay when a dexmedetomidine group was compared to remifentanil group in patients undergoing spine surgery. The prolonged PACU stay was attributed to the oversedation effect of dexmedetomidine. It was described that the oversedation effect of dexmedetomidine can be avoided by a timely cessation or by tapering of the maintenance infusion.

There was no significant difference in PACU opioid consumption. Aronsohn et al, compared OFA to standard opioid technique in patients undergoing bariatric surgery. There was no significant difference in PACU opioid consumption.

There was a significant difference in the incidence of nausea and vomiting between both groups, as more patients in the opioid based group experienced these two specific side effects. Frauenknecht et al, reported that opioid inclusive anesthesia is associated with increased postoperative nausea and vomiting. Among the OFA regimen used in our study, dexmedetomidine has antiemetic effects which may result from inhibition of the sympathetic nervous system and catecholamine release by its action on α2-adrenoreceptors. A review reported that dexmedetomidine, when administered as a continuous infusion, reduces postoperative nausea and vomiting.
Our study is limited in that it was done in a single tertiary center in Lebanon which may limit our ability to extrapolate or generalize our findings. Another limitation is the constant infusion rate of dexmedetomidine compared to a variable remifentanil infusion rate, which resulted in the use of more antihypertensive medications in the OFA group to control the hemodynamic fluctuations in some patients. A future approach could be to adjust the protocol to allow a variation in the dexmedetomidine maintenance infusion rate (0.2–0.5 mcg/kg/hr instead of 0.3mcg/kg/hr).

**Conclusion**

In summary, the use of opioid-free anesthesia in patients undergoing major spine surgery leads to reduced postoperative morphine use in the first 24 hours, reduced postoperative nausea and vomiting within 48 hours and intraoperative hemodynamic stability. As such, opioid-free anesthesia is suitable for patients with high risk of opioid-related complications, specifically patients with chronic pain conditions undergoing major spine surgery who can benefit from intraoperative low dose of dexmedetomidine, lidocaine and ketamine. Further research about long term analgesic effects of dexmedetomidine beyond first postoperative 24 hours, along with adaptation of the anesthesia regimen used in this study as a form of opioid-free anesthesia is warranted.

**Abbreviations**


**Declarations**

**Ethics approval and consent to participate**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study was conducted with the approval from Institutional Review Board (IRB) of the Lebanese American University (LAU) (LAUMCRH.HB1.11/01/2018) and was registered with ClinicalTrials.gov (registration number: NCT03417193) and posted on 31/01/2018.

Confirming informed consent was obtained from all study participants. Moreover, all methods were carried out in accordance with relevant guidelines and regulations.

**Consent for publication**

Not applicable.
Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors’ Contributions

HB: Reviewed the relevant literatures, designed, and conducted the study, analyzed data, wrote the first draft of the paper, and approved the final version of the manuscript for submission. LG: Reviewed the relevant literatures, recruited patients, collected data, analyzed data, and wrote the first draft of the paper. JAN: Recruited patients and collected data. VYK: Reviewed and approved the final version of the manuscript for submission. RAN: Recruited patients, collected data, edited, and approved the final version of the manuscript for submission.

All authors have read and approved the final manuscript and agreed with its submission to BMC Anesthesiology.

Acknowledgments

Not applicable

References


**Figures**
Figure 1
Flow diagram