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ANESTHESIA CONSIDERATIONS FOR INTRATHECAL NARCOTIC UTILIZATION FOR  
A CESAREAN SECTION PATIENT

by

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Bachelor of Science in Nursing, Southern Illinois University Edwardsville, 2010

An Independent Study

Submitted to the Graduate Faculty

of the

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## PERMISSION

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Department    Nursing

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## ABSTRACT

**Title:** Anesthesia Considerations for Intrathecal Narcotic Utilization for a Cesarean Section Patient

**Background:** A subarachnoid block for an elective cesarean section procedure is a frequent anesthetic delivered by anesthesia professionals. The addition of a narcotic to the SAB is becoming a common practice, but hesitancy remains due to the potential adverse effects from these narcotics, and thus is not a standard of care in the anesthesia profession. Of note, the terms “subarachnoid block” and “intrathecal” pertain to the same anatomical space and often used interchangeably. However, “subarachnoid block” in this paper relates to the local anesthetic alone or in combination with a narcotic and used interchangeably with the term “spinal.” The term “intrathecal” is used to describe the narcotic medication.

**Purpose:** The purpose of this independent project is to review current literature on the use of intrathecal narcotics, specifically preservative-free morphine and fentanyl, during cesarean sections to determine if there is one superior agent, or if a combination yields superiority. A second purpose is to determine an ideal dose and if the benefits of analgesia outweigh the potential adverse effects of these agents.

**Process:** A comprehensive review of the literature was conducted using CINAHL, PubMed, and Scopus databases from the University of North Dakota Library Health Sciences Library. Preference was given to those articles and studies occurring in the past five years, but relevant material was found beyond this time period and included in the literature review. These findings were analyzed to help support the results of this project.

**Results:** The addition of an intrathecal narcotic to a subarachnoid block (SAB) during cesarean sections has been shown to have positive outcomes. However, clarity regarding morphine alone or in combination with fentanyl remains ambiguous. Additionally, dosing of these two medications is unclear. Morphine provides extended post-operative analgesia, but is limited in the intraoperative phase due to its slow onset of action. Fentanyl has been shown to be beneficial in the intraoperative phase, but has little effect in the post-operative phase. Both medications expose the patient to adverse effects and potentially life-threatening complications. Decisions regarding utilization should be based on a thorough discussion with each patient and individualized to meet their expectations and desires.

**Implications:** Intrathecal narcotics are beneficial during cesarean sections. The utilization of intrathecal narcotics, either alone or in combination, should be evaluated on an individual patient basis as the anesthesia professional develops their plan of care.

**Keywords:** cesarean section, spinal anesthesia, narcotic, morphine, fentanyl, intrathecal, post-operative

## **Anesthesia Considerations for Intrathecal Narcotic Utilization for a Cesarean Section Patient**

Every year, cesarean sections account for a large percentage of the total anesthetic cases anesthesia professionals are required to provide. In 2016, the United States registered a total number of 3,945,875 births, of which 31.9% were via cesarean section (Martin, Hamilton, Osterman, Driscoll, & Drake, 2018). Regional anesthesia via the subarachnoid block (SAB) is a primary method to achieve surgical anesthesia for scheduled cesarean sections. The debate on whether the addition of an intrathecal narcotic dose to the SAB remains open and varied among anesthesia practitioners. The potential benefits of reduced post-operative pain must be weighed against the potential adverse effects such as pruritus, nausea/vomiting, and respiratory depression.

Spinal anesthesia has been utilized for cesarean section cases for decades. The SAB offers many advantages over a general anesthetic, including relatively quick and easy performance, rapid onset of action, decreased mortality risk to mother, more alert neonate at birth, sooner mother-neonate bonding, and better postoperative pain control (Butterworth, Mackey, & Wasnick, 2013). In fact, a general anesthetic carries a 16.7 times greater risk of maternal death compared with regional anesthesia (Nagelhout & Plaus, 2014). The American Society of Anesthesiologists (ASA) Task Force on Obstetric Anesthesia recommends a neuraxial technique over a general anesthetic in most cesarean section circumstances (Apfelbaum et al., 2015). For these reasons mentioned above, knowledge on different intrathecal combinations will allow the anesthesia professional to provide an adequate anesthetic while optimizing patient satisfaction.

### **Purpose**

The purpose of this independent project is to provide anesthesia professionals with evidence-based research regarding intrathecal narcotic, specifically morphine and fentanyl, utilization during spinal anesthesia in cesarean sections. With no standard of care regarding the issue, practice patterns are often based on school training, facility protocols, or prior experiences. This paper is a culmination of extensive literature research in hopes to provide sufficient evidence, which enables the anesthesia professional to determine whether or not the addition of narcotics, either alone or in combination, into a SAB during a cesarean section is beneficial.

### **Case Report**

This case involved a 35-year-old, 114 kg, 167 cm, BMI 41 kg/m<sup>2</sup>, female patient scheduled for an elective laparotomy cesarean section due to breech position of baby. She was a gravida 2 para 1, measuring 37 weeks and 4 days. Her medical history was significant for hypertension, headaches, and gestational diabetes. She had no significant surgical history and had received an epidural with her first vaginal delivery. Her medications included methylodopa, metformin, and prenatal vitamins.

Her pre-op evaluation was normal other than the above listed medical history and she was assigned an ASA physical status level two. An airway evaluation revealed a Mallampati score of 2, thyromental distance of 3 fingerbreadths, normal dental exam, and full neck mobility. She had no history of back surgery, spinal abnormalities, or significant coagulopathies. Informed consent was obtained to proceed with a spinal anesthetic with the addition of both duramorph (preservative-free morphine) and fentanyl.

She was brought to the operating room (OR) suite with Lactated Ringer's (LR) already infusing, connected to standard anesthesia monitors including non-invasive blood pressure,

electrocardiogram, and pulse oximetry (SpO<sub>2</sub>). Initial vital signs included blood pressure 135/86, heart rate 88/min, respirations 20/min, SpO<sub>2</sub> 94% on room air. O<sub>2</sub> was administered via simple mask at 5 L/min with end tidal carbon dioxide (ETCO<sub>2</sub>) monitoring. The patient was positioned in a sitting position on the OR table, appropriate landmarks were identified on patient's lower back, and the area was prepped with betadine in the normal sterile fashion. An initial skin wheel with 1% lidocaine was made at the lumbar (L)3-4 level with subsequent introduction of the spinal introducer needle. The subarachnoid space was obtained via a 25 gauge, 3.5 inch pencil point Pencan needle. Proper placement was confirmed with the presence of free-flowing cerebrospinal fluid (CSF) and the absence of blood. Medication administration followed with 0.75% hyperbaric bupivacaine 12 mg, fentanyl 10 mcg, and duramorph 0.15 mg.

The patient was immediately positioned in the supine position with left uterine tilt to prevent aortocaval compression and supine hypotension. A time of 2-3 minutes was given in order for the SAB to set-up. Vital signs were monitored every two and half minutes. Upon checking dermatomal level of block, it was found the patient had decreased temperature sensation to the umbilicus level correlating to a thoracic (T)10 region. A Foley catheter was inserted via the nurse without complaints from the patient. However, at this point in time, complaints of an itching sensation to the patient's face was noted. Patient was informed this can be an adverse effect from narcotic administration contained in the spinal. Following the catheter insertion, a recheck of the dermatomal level blockade was assessed and found to be at a level correlating with the T4 dermatome. The patient was monitored closely to ensure blockade level was not progressing too far cephalad. Cefoxitin 2 grams was administered prior to incision. The patient denied any difficulty breathing and denied feeling abdominal pinch by surgeon at which time an adequate SAB was determined and the surgeon made the surgical incision.



The perioperative phase was uneventful. There were no significant decreases in blood pressure and the patient denied any nausea/vomiting feelings. A healthy baby was delivered without complications with Apgar scores 8 and 8 at 1 and 5 minutes respectively. After delivery of the placenta, 20 units oxytocin was injected into her hanging LR liter bag. Other medications given post-delivery included intravenous (IV) ondansetron 4 mg, diphenhydramine 12.5 mg, dexamethasone 4 mg, and ketorolac 30 mg. Total IVF administration was 1,200 ml with an estimated blood loss of 700 ml and urine output of 50 ml. Of note, patient never complained of pruritus sensation other than one instance mentioned previously.

The patient's post-operative phase included one episode of mild hypoglycemia with a blood glucose level of 73 mg/dL in which she was given apple juice. Recheck blood glucose revealed a level of 142 mg/dL. It was standard practice at our facility to place post-operative cesarean section patients on scheduled ketorolac 30 mg every 6 hours if no contraindications existed. She was given this medication as scheduled and discharged home on post-operative day 2. She required no additional pain medications during her stay.

### **Literature Search**

A comprehensive review of the published literature was conducted using the following databases: PubMed, Scopus, AccessMedicine, Cochrane Database of Systemic Reviews, Cumulative Index of Nursing and Allied Health (CINAHL), and the Journal of the American Society of Anesthesiologists. The databases were accessed using the University of North Dakota Health Sciences Library. Keyword and search terms included *cesarean section*, *spinal anesthesia*, *intrathecal*, *narcotic*, *morphine*, *fentanyl*, and *post-operative* in different combinations. Exclusion criteria were non-English articles, articles reporting epidural information, and articles reporting information pertaining to opioids other than morphine or

fentanyl. Preference was given to those studies and articles occurring within the past five years, however relevant articles outside this time frame were reviewed and included in this paper.

PubMed was the first database searched using MeSH (medical subject headings) terms: *cesarean section AND post-operative pain*, which resulted in 863 articles. A limit of 5 years was placed on the search criteria which reduced the number of articles to 145. A quick review of the titles yielded three articles that potentially were related to the topic. These abstracts were reviewed and met inclusion criteria.

A secondary search of PubMed was then undertaken. The MeSH technique was aborted for an advanced search using the terms *cesarean section AND spinal anesthesia AND morphine AND fentanyl* in different combinations. The end result yielded seven new articles that met inclusion criteria for this review.

Scopus was the second database searched for this literature review. A search using the terms *cesarean section AND spinal anesthesia AND intrathecal AND narcotic AND morphine* in different combinations yielded two new articles. These searches produced a number of irrelevant articles, of which were determined based on article title. If an article title was related to the topic, the abstract was then reviewed to determine inclusion or exclusion.

AccessMedicine was accessed for the purpose of providing foundational information on spinal anesthesia and intrathecal narcotics. A quick, separate search using the terms *spinal anesthesia* and *intrathecal narcotic* produced text books containing relevant information. One text encompassing information regarding both spinal anesthesia and intrathecal narcotic information was chosen for inclusion.

The databases CINAHL and Cochrane were also searched for relevant articles. However, using the search terms mentioned previously, no new articles were discovered. Therefore, no

articles were used from those databases in this independent project. The end result of the literature search produced twelve articles that met inclusion criteria for this independent project. These articles were carefully reviewed and provide the material and evidence to support this paper.

## **Review of Literature**

### **Pathophysiology**

Spinal anesthesia is accomplished by injecting local anesthetic into the CSF contained within the subarachnoid space. According to Butterworth, Mackey, & Wasnick (2013), the adult spinal cord terminates at level correlating to the L1 space. Therefore, a SAB at a level of L2 or lower is safe to avoid spinal cord puncture, however, most anesthesia professionals initially attempt puncture at level correlating to L3 or lower. A reassuring aspect of spinal anesthesia is the confirmatory placement of a needle with free-flowing CSF. However, the anatomy should be kept in mind when performing a SAB.

Butterworth, Mackey, & Wasnick (2013) outline the layers of the spinal cord and associated ligaments the needle passes through prior to the subarachnoid space. The spinal cord meninges include the pia mater, arachnoid mater, and dura mater. The pia mater is adherent to the spinal cord, which is then covered by the arachnoid mater, and finally the dura mater. The ligaments, working from the skin to the dura mater, include the supraspinous ligament, the interspinous ligament, and the ligamentum flavum.

The nerve root is the principal site of action during a subarachnoid block. CSF is in direct contact with these nerve roots, thus a relatively small local anesthetic dose and volume can achieve a dense sensory and motor block. Sensory blockade is the result of local anesthetic interacting with the posterior nerve roots. Motor blockade is the opposite and correlates with

blockade of the anterior nerve roots. Autonomic blockade is also associated with this anterior nerve root block, which is responsible for the sympathetic blockade (Butterworth, Mackey, & Wasnick, 2013).

According to Catterall and Mackie (2018), sympathetic nerve fibers leave the spinal cord between T1 and L2. The cephalad spread of local anesthetic in the CSF blocks these sympathetic fibers, resulting in unopposed parasympathetic activity and accounts for the hypotension associated with a SAB. Cardiac accelerator fibers exist at T1-T4 and if a block progresses to this height, an inability to maintain cardiac output could result, leading to cardiac compromise.

An important understanding related to local anesthetics is that of nerve fiber sensitivity and differential block. Simplistically, nerves are separated into three groups—A, B, and C. Nerve diameter and myelination are differentiating characteristics of these groups. A fibers are generally larger with heavy myelination and further broken into four subcategories: A-alpha, A-beta, A-gamma, and A-delta. B fibers are intermediate in size and lightly myelinated. C fibers are the smallest with no myelination. Larger, myelinated nerves are more resistant to local anesthetics, whereas small, unmyelinated fibers are more sensitive. Thus, a general sequence of spinal nerve inhibition follows autonomic (type B) nerves, to sensory (type C and A-delta, gamma, & beta) nerves, to motor (type A-alpha) nerves (Nagelhout & Plaus, 2014). However, local anesthetic blockade of these nerve fibers does not fully guarantee a pain free anesthetic.

The perception and understanding of pain is complex and beyond the scope of this paper, however, a brief explanation can facilitate a fundamental reason for the administration of opioids intrathecally. The first intrathecal opioid study occurred in 1979 and involved 2 mg of morphine being injected into the SAB (Gomez & Garzon, 2015). First pain processing synapses occur in the dorsal horn of the spinal cord. Direct injection of narcotics here provides a rapid, dense

analgesic affect with significantly less medication compared to an oral or parenteral route (Yaksh & Wallace, 2018). The advantage of using an intrathecal narcotic in a SAB is relieving visceral pain often not covered solely by a local anesthetic, and possibly prolonging the sensory block without affecting motor or sympathetic function (Nagelhout & Plaus, 2014). However, these advantages do not come without risks, which will be discussed later in the paper.

A brief review of opiate receptors warrants discussion when explaining intrathecal narcotics. Opiate receptors are divided into mu ( $\mu$ ), kappa ( $\kappa$ ), and delta ( $\delta$ ). Mu is further classified into  $\mu$ -1 and  $\mu$ -2. Each subtype, when activated, displays differentiating characteristics. For instance,  $\mu$ -1 activation displays supraspinal analgesia, euphoria, miosis and urinary retention.  $\mu$ -2 is responsible for spinal analgesia, respiratory depression, bradycardia, constipation and dependence.  $\kappa$  activation results in spinal analgesia, dysphoria, and sedation.  $\delta$  activation displays spinal analgesia, respiratory depression, and physical dependence. These receptors are primarily located in the substantia gelatinosa, lamina II of the dorsal horn. Mu receptor analgesia is believed to function on the descending pain pathway via a GABA (gamma-aminobutyric acid) mediation. Kappa receptor analgesia functions via an inhibition of substance P. The exact analgesia function of delta is not entirely understood (Nagelhout & Plaus, 2014).

### **Pharmacology**

Medications used within the neuraxial space should all be preservative free agents. The addition of certain preservatives can be potentially neurotoxic and could cause spinal cord injury. Proper identification of preservative-free medications should be part of the anesthesia professional's checklist prior to performing a SAB.

Morphine is a hydrophilic agent with interaction on all three opioid receptors. The hydrophilic characteristic results in delayed onset of action and prolonged duration of action

when compared to fentanyl. This prolonged duration of action however, is the characteristic that distinguishes morphine as an ideal agent to control postoperative pain in cesarean section operations. Morphine also exhibits a greater cephalocaudal spread, which potentially increases effects on the brainstem, placing patients at increased risk for respiratory depression (Yaksh & Wallace, 2018).

Fentanyl is a lipophilic agent with interaction of opioid receptors similar to morphine. The lipophilicity nature allows diffusion across spinal membranes resulting in a rapid onset of action. However, this characteristic also results in vascular absorption and increased serum concentrations leading to faster elimination times (Yaksh & Wallace, 2018). This rapid onset of action has created an argument for fentanyl use in the perioperative period to help decrease visceral pain not typically covered by local anesthetics or intrathecal morphine.

### **Subarachnoid Block**

A plain local anesthetic agent was the primary choice for a subarachnoid block during a cesarean section for many years. It was not until the 1980s that intrathecal narcotics became a widely used technique (Sultan, Halpern, Pushpanathan, Patel, & Carvalho 2016). This discovery resulted in a number of benefits for the parturient patient. The synergistic effect of the combined local anesthetic and opioid yielded improved analgesia with attenuated side effects (Nagelhout & Plaus, 2014).

In a double-blinded, randomized, controlled prospective study involving fifty parturients by Venkata, Pasupuleti, Pabba, Porika, & Talari (2015), it was discovered that a conventional, plain bupivacaine dose produced significantly more intraoperative hypotension, prolonged time period to reach a T6 sensory block, and decreased postoperative analgesia when compared to a combined bupivacaine/fentanyl dose. The ability to use less local anesthetic in the combined

method decreases the sympathetic segmental block, which is responsible for the hypotension associated with SAB.

Onishi, Murakami, Hashimoto, & Kaneko (2017) support this in their study comparing different bupivacaine doses. The prospective double-blind randomized trial involved seventy subjects using doses of 6-12 mg of 0.5% bupivacaine in combination with morphine and fentanyl to determine which dose achieved adequate intraoperative analgesia without the need for postoperative epidural supplementation. They found increasing bupivacaine doses resulted in a significant trend in the use of phenylephrine and incidence of nausea/vomiting both related to hypotension.

### **Morphine**

As mentioned previously, a combination of morphine and bupivacaine is a common practice for a SAB during a cesarean section. Throughout the literature, there are a number of research articles advocating for the use of intrathecal morphine in a SAB during a cesarean section. Its use has been supported to decrease post-operative pain and improve patient satisfaction. However, its use alone or in combination with fentanyl remains debatable and the exact dosing remains inconclusive in the literature. This lack of clarity and potential adverse effect of respiratory depression creates hesitancy in its use.

Whether morphine is utilized alone or in combination with fentanyl in the SAB is highly variable. Siti Salmah & Choy (2009) performed a study that found morphine to be superior to that of fentanyl. This finding was based on significantly lower visual analogue scores (VAS) at post-operative hours 6, 12, 18, and 24. This prospective, randomized controlled, single-blind study involved sixty participants split into two groups, receiving either a bupivacaine/morphine SAB or bupivacaine/fentanyl SAB. Those who received a morphine/bupivacaine combination

used less post-operative cumulative morphine via a patient-controlled analgesia (PCA) machine and had a longer period of time to first PCA use.

Thorton, Hanumanthaiah, O'Leary, & Iohom (2015) echo this finding in their case-controlled, double-blinded study involving fifty patients. They found the use of fentanyl combined with morphine and bupivacaine is unwarranted as post-operative VAS at 4 hours were not significantly different and side effects were more common with the addition of fentanyl.

A separate study by Karaman, Günösen, Uyar, Biricik, & Firat (2010) advocates for a pure morphine/bupivacaine SAB. They utilized a random double-blind controlled trial comparing three separate groups, morphine/bupivacaine (20 patients), fentanyl/bupivacaine (20 patients), and morphine/fentanyl/bupivacaine (20 patients), and concluded morphine was superior to that of fentanyl, and the combination of morphine/fentanyl/bupivacaine resulted in no added benefits over morphine alone. This conclusion was based on similar block height of T4 dermatome, time for block onset, intraoperative pain scores, and occurrence of side effects. Additionally, the morphine/bupivacaine group had a significantly longer period post-operatively to the time of first analgesic request. This however, was based on what is considered a high dose of morphine at 200 mcg.

The exact dose of the adjunct morphine became a key aspect in this literature review. With no standard on the exact dose, a multitude of dosages have been trialed in studies. Carvalho & Tenório (2013) performed a randomized control, double-blind study involving one hundred twenty-three pregnant women undergoing a cesarean section. They separated the women into two groups, one group receiving 0.5% bupivacaine 12 mg with morphine 50 mcg, and the other receiving 0.5% bupivacaine 12 mg with morphine 100 mcg. They found no statistical difference in moderate/severe post-operative scores between the groups. They concluded morphine 50 mcg



in combination with bupivacaine was a sufficient adjunct for cesarean sections, mainly because there was no added analgesia with the higher dose and side effects were more frequently encountered with the 100 mcg dose. However, this study specifically only observed pain scores between the 9<sup>th</sup> and 11<sup>th</sup> hours and 22<sup>nd</sup> and 24<sup>th</sup> hours postoperatively.

In comparison, Wong, Carvalho, & Riley (2013) undertook a retrospective chart review of 241 patients at their facility after changing from a SAB combination involving morphine 200 mcg to a combination involving only morphine 100 mcg. They found patients receiving the combination with morphine 200 mcg had better postoperative analgesia and consumed less rescue opioids in the first 24-hour post-operative period. However, incidents of nausea and anti-emetic use were also greater in this group.

A meta-analysis by Sultan, Halpern, Pushpanathan, Patel, & Carvalho (2016) found similar results. They reviewed eleven articles comparing a SAB containing low-dose (LD) morphine, 50-100 mcg to a SAB containing high-dose morphine, >100-250 mcg. Patient distribution included 233 in the HD group and 247 in the LD group. They discovered an insignificant difference in post-operative pain scores and morphine consumption at the 12 and 24-hour time periods. However, the HD group had a median time of 4.49 hours longer before time to first analgesic request. This extended pain relief came at the expense of increased pruritus, nausea/vomiting, and antiemetic use. Potential side effects contribute significantly in the decision to use an intrathecal narcotic, but none are more serious than respiratory depression.

Intrathecal morphine utilization remains cautious due in large part to the association with delayed respiratory depression. The exact definition of respiratory depression differs throughout the literature with some studies defining it as a respiratory rate less than 10, others defining it as a respiratory rate less than 8 and others defining it as a SpO<sub>2</sub> less than 90% for a varying amount

of time. The unreliable definition makes the exact incidence difficult to compute, but has been reported as low as 0-0.26% (Ladha, Kato, Tsen, Bateman, & Okutomi 2017). The high levels of progesterone in the obstetric patient theoretically combats respiratory depression by stimulating the respiratory system, increasing minute ventilation, decreasing the PaCO<sub>2</sub> and causing a mild respiratory alkalosis (Gómez & Garzón, 2015).

Ladha, Kato, Tsen, Bateman, & Okutomi (2017) undertook a prospective study which included 731 cesarean patients receiving a SAB containing 0.5% bupivacaine 2.4 mL, fentanyl 10 mcg and morphine 150 mcg. They used continuous pulse oximetry in the first 24 hours post-operatively to assess mild desaturation (SpO<sub>2</sub> less than 90%) and severe desaturation (SpO<sub>2</sub> less than 85%). If a patient experienced a time period lasting 30 seconds or longer it was recorded as an event. They found 23% patients experienced one mild desaturation, 13% experienced 2 or more mild desaturations and 4% experienced a severe desaturation. These events occurred most often in the 4-12 hours post-operatively. These statistics demonstrate the incidence of respiratory depression may be higher than reported in the literature.

### **Fentanyl**

Fentanyl has become a more common adjunct in the SAB during a cesarean section. Its rapid onset of 5-10 minutes compared to morphine's onset of 60-90 minutes and short duration of action produces favorable intraoperative analgesia and immediate post-operative utilization. Weigl et al. (2016) performed a double-blind, prospective, randomized controlled study specifically utilizing fentanyl in the SAB during cesarean sections. They separated thirty parturient patients into a control group receiving bupivacaine and saline and twenty-nine parturient patients into the fentanyl group receiving fentanyl 25 mcg in their SAB. They defined the first 12 hours post-operatively as the most painful period, based on the control groups

supplemented analgesics needs. They found the fentanyl group had less intraoperative pain scores and less rescue medication in the first 12 hours post-operatively. However, between the 12-24 hour period, pain scores were similar in the two groups and did not show a reduction in post-operative opioid use. They concluded the fentanyl 25 mcg dose prolonged effective analgesia averaging between 3 to 5 hours which is similar to other study findings. They also found that doses greater than 10 mcg have abolished intraoperative visceral pain in almost all cases, but as one decreases the fentanyl dose, a shorter analgesic duration is noted post-operatively.

The side effect profile associated with intrathecal fentanyl has been reported to be less than intrathecal morphine. This is likely due to its lipid solubility and increased absorption into neural tissue, decreasing cephalad spread (Nagelhout & Plaus, 2014). Nausea/vomiting, pruritus, and respiratory depression are all potential risks associated with intrathecal fentanyl as they are adverse effects of all opioids. However, the literature has indicated the percentages are much lower than those associated with intrathecal morphine usage. In the study by Weigl et al. (2016), they found percentages of nausea/vomiting and pruritus to be 7% and 10% respectively, which are similar to other studies. They also acknowledge that respiratory depression associated with lipophilic agents is rare and mostly associated with sufentanil. However, it is a potential devastating consequence leading to increased mortality and morbidity, and therefore should be assumed it can occur.

### **Morphine & Fentanyl Combination**

The long acting duration of intrathecal morphine and quick onset of intrathecal fentanyl makes one assume that a combination of the two in a SAB would produce optimal analgesia during a cesarean section. As outlined earlier, intrathecal fentanyl has a relatively quick onset

and reduces perioperative pain associated with visceral sensation and excessive uterine manipulation. Intrathecal morphine has an extended duration of action and can reduce rescue opioid usage up to 18-24 hours post-operatively. However, these ideal characteristics are not always observed in actual practice.

Weigl et al. (2017) performed a second randomized control study comparing a SAB containing intrathecal fentanyl and morphine (FM group) to that of intrathecal morphine (M group) alone. Sixty patients were divided evenly into each group, with the FM group receiving bupivacaine supplemented with morphine 100 mcg and fentanyl 25 mcg, and the M group receiving bupivacaine supplemented only with morphine 100 mcg. While the M group required more intra-operative analgesics, the FM group required more than double the dose of demerol, which was used as a rescue agent via PCA, in the first 1-12 hours post-operatively. The concept of acute spinal opioid tolerance with small dose fentanyl has been reported. Another explanation outlined is that of the fast-acting intrathecal fentanyl binding to spinal opioid receptors thus leaving a smaller percentage of receptors for intrathecal morphine to act upon. When the short acting fentanyl has dissipated, there is less morphine available due to the higher metabolization from increased free levels. This then leads to an increased sensation of pain.

The side effect profile associated with a combination of intrathecal morphine and fentanyl is a main deterrent from its use. The incidence of both nausea/vomiting and pruritus increased with a combination technique.. Weigl et al. (2017) reported a 37% incidence of nausea/vomiting and 36% incidence of pruritus in a combination method. They acknowledge these findings are congruent with those found in other studies reviewing a combination technique, reporting a percentage of 20-35% incidence of nausea/vomiting and 40-63%

incidence of pruritus. Respiratory depression was not observed in their study and found to be rare in the literature and no depressed neonatal Apgar scores were noted.

### **Discussion**

The patient in this case review was undergoing an elective laparotomy cesarean section. She had no significant history or bleeding diathesis excluding her from a spinal anesthetic. She was consented for a subarachnoid block with the addition of both morphine and fentanyl in combination with hyperbaric bupivacaine.

An atraumatic spinal was successfully completed with subsequent injection of fentanyl 10 mcg, duramorph 0.15 mg, and 0.75% bupivacaine 12 mg. Upon assessing block height, a sensory block correlating to a T4 dermatome was noted. The patient did complain of mild pruritus to her face, but otherwise was pain free with no complaints of nausea or vomiting. Hypotension was not observed. An uneventful procedure ensued with a healthy baby being born with APGAR scores 8 and 8 at 1 and 5 minutes respectively. Patient was given prophylactic antiemetics once baby was extracted and a non-steroidal anti-inflammatory agent with incision closure.

The SAB “cocktail” utilized in this case report is congruent with current literature findings. A combination of intrathecal fentanyl and morphine with hyperbaric bupivacaine has demonstrated positive results in parturient patients undergoing a cesarean section. The patient did experience one episode of pruritus intraoperatively, which resolved prior to leaving the operating room. The patient was monitored with continuous pulse oximetry for 24 hours post-operatively. No respiratory depression was noted in that time frame and she was subsequently discharged home on POD 2. Standard procedure was for post-operative cesarean section patients

to receive ketorolac 30 mg every 6 hours around the clock. Rescue analgesics were available upon patient request, but none were needed in this case.

### **Recommendations**

A handful of recommendations are warranted based off this case study and literature review. First, the utilization of an intrathecal narcotic in combination with hyperbaric bupivacaine in a SAB during a cesarean section is beneficial. Second, the sole use of intrathecal fentanyl in the SAB is suggested against due to limited post-operative analgesia. Third, a SAB with hyperbaric bupivacaine and preservative-free morphine at a dose between 100-150 mcg alone or in combination with fentanyl 10-25 mcg provides adequate analgesia for a cesarean section. Fourth, if utilizing intrathecal morphine in the SAB, nursing staff should be adequately trained, and a protocol for monitoring and treatment of complications, specifically delayed respiratory depression, should be in place. Lastly, a thorough discussion with each patient should precede the determination of the SAB mixture to ensure the patient is aware of potential benefits and possible adverse effects associated with certain medications.

Due to the varying techniques and protocols established at different institutions, the fortifying evidence for intrathecal utilization in a SAB during a cesarean section is difficult to label 100 percent efficacious. A number of different post-operative protocols to help reduce pain associated with cesarean sections were noted within the literature. These likely have a prominent influence on determining just how effective an intrathecal narcotic additive really is in a SAB. Also, many of the studies reviewed had relatively small sample sizes. Although, the power was determined to be adequate within these studies, larger scale studies would be recommended in the future. Another aspect researchers may consider would be to separate woman presenting for a

first cesarean section versus those with a repeat cesarean section to assess how pain scores differentiate and the effect intrathecal narcotics in the SAB have on each situation.

### **Conclusion**

The practice of instituting a combined intrathecal narcotic and local anesthetic for a subarachnoid block during cesarean sections appears beneficial in most instances. The combined method of bupivacaine/morphine seems appropriate for most patients. This combination provides adequate post-operative pain up to 24 hours. Respiratory depression is a serious, but infrequent side effect. Appropriate monitoring is essential for these patients. The combination of bupivacaine/morphine/fentanyl is also an acceptable practice. However, this significantly increases the risk of side effects such as pruritus, nausea and vomiting. A balance between analgesia and potential risks must be carefully evaluated by the anesthesia professional.

A thorough discussion with the patient is the most important aspect in determining the spinal anesthetic combination plan. Tailoring a plan to meet individual needs and expectations is the essence of our practice, especially in a controlled and life changing event like a cesarean section. A discussion outlining pain control versus potential adverse risks allows the patient to make a consented decision based on their wishes and optimizes patient satisfaction.

## References

- Apfelbaum, J.L., Hawkins, J.L., Agarkar, M., Bucklin, B.A., Connis, R.T., Gambling, D.R., Mhyre, J., Nickinovich, D.G., Sherman, H., Tsen, L.C., & Yaghmour, E.A. (2016). Practice guidelines for obstetric anesthesia: An updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia and the Society of Obstetric Anesthesia and Perinatology. *Anesthesiology*, *124*(2), 1-31. Retrieved from <http://anesthesiology.pubs.asahq.org/article.aspx?articleid=2471779>
- Butterworth, J.F., Mackey, D.C., & Wasnick, J.D. (2013). *Morgan & Mikhail's clinical anesthesiology* (5<sup>th</sup> ed.). McGraw Hill Education: Chicago, IL
- Carvalho, F.A. & Tenório, S.B. (2013). Comparative study between doses of intrathecal morphine for analgesia after caesarean. *Brazilian Journal of Anesthesiology*, *63*(6), 492-499. doi:10.1016/j.bjane.2013.01.001
- Catterall, W.A. & Mackie, K. Local Anesthetics. In: Brunton, L.L., Hilal-Dandan, R., & Knollman, B.C. (2018). *Goodman & Gilman's: The pharmacological basis of therapeutics* (13<sup>th</sup> ed.). McGraw Hill Education: New York, NY. Retrieved from <https://accessmedicine-mhmedical-com.ezproxy.library.und.edu/content.aspx?sectionid=170106799&bookid=2189&jumpsectionID=172477517&Resultclick=2#1149947580>
- Gomez, P.J.H. & Garzon, J.F. (2015). Intrathecal opioids and respiratory depression: Is it myth in obstetrics? *Colombian Journal of Anesthesiology*, *43*(1), 101-103
- Karaman, S., Günösen, I., Uyar, M., Biricik, E., & Firat, V. (2010). The effects of morphine and fentanyl alone or in combination added to intrathecal bupivacaine in spinal anesthesia for



- cesarean section. *The Journal of the Turkish Society of Algology*, 23(2), 57-63.  
doi:10.5505/agri.2011.44127
- Ladha, K.S., Kato, R., Tsen, L.C., Bateman, B.T., & Okutomi, T. (2017). A prospective study of post-cesarean delivery hypoxia after spinal anesthesia with intrathecal morphine 150µg. *International Journal of Obstetric Anesthesia*, 32(1), 48-53.  
doi:10.1016/j.ijoa.2017.06.003
- Martin, J.A., Hamilton, B.E., Osterman, M.J.K., Driscoll, A.K., & Drake, P.D. (2018). Births: Final data for 2016. *National Vital Statistics Reports*, 67(1), 1-12. Retrieved from [https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67\\_01.pdf](https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_01.pdf)
- Nagelhout, J.J. & Plaus, K.L. (2014). *Nurse anesthesia* (5<sup>th</sup> ed.). Elsevier Saunders: St. Louis, MO
- Onishi, E., Murakami, M., Hashimoto, K., & Kaneko, M. (2017). Optimal intrathecal hyperbaric bupivacaine dose with opioids for cesarean delivery: A prospective double-blinded randomized trial. *International Journal of Obstetric Anesthesia*, 31, 68-73.  
doi:10.1016/j.ijoa.2017.04.001
- Siti Salmah, G. & Choy, Y.C. (2009). Comparison of morphine with fentanyl added to intrathecal 0.5% hyperbaric bupivacaine for analgesia after caesarean section. *The Medical Journal of Malaysia*, 64(1), 71-74. Retrieved from [http://www.e-mjm.org/2009/v64n1/Intrathecal\\_Morphine.pdf](http://www.e-mjm.org/2009/v64n1/Intrathecal_Morphine.pdf)
- Sultan, P., Halpern, S.H., Pushpanathan, E., Patel, S., & Carvalho, B. (2016). The effect of intrathecal morphine dose on outcomes after elective cesarean delivery: A meta-analysis. *Anesthesia & Analgesia*, 123(1), 154-164. doi:10.1213/ANE.0000000000001255


- Thornton, P., Hanumanthaiah, D., O'Leary, R.A., & Iohom, G. (2015). Effects of fentanyl added to a mixture of intrathecal bupivacaine and morphine for spinal anesthesia in elective caesarean section. *Romanian Journal of Anaesthesia and Intensive Care*, 22(2), 97-102. Retrieved from <https://www.ncbi.nlm.nih.gov.ezproxy.library.und.edu/pmc/articles/PMC5505381/>
- Venkata, H.G., Pasupuleti, S., Pabba, U.G., Porika, S., & Talari, G. (2015). A randomized controlled prospective study comparing a low dose bupivacaine and fentanyl mixture to a conventional dose of hyperbaric bupivacaine for cesarean section. *Saudi J Anaesth*, Apr-Jun9(2), 122-127. doi:10.4103/1658-354X.152827
- Weigl, W., Bierylo, A., Wielgus, M., Krzemien-Wiczynska, S., Szymusik, I., Kolacz, M., & Dabrowski, M.J. (2016). Analgesic efficacy of intrathecal fentanyl during the period of highest analgesic demand after cesarean section: A randomized controlled study. *Medicine*, Jun95(24), 1-7. doi:10.1097/MD.0000000000003827
- Weigl, W., Bierylo, A., Wielgus, M., Krzemien-Wiczynska, S., Szymusik, I., Kolacz, M., & Dabrowski, M.J. (2017). Perioperative analgesia after intrathecal fentanyl and morphine or morphine alone for cesarean section: A randomized controlled study. *Medicine*, May96(48), 1-7. doi:10.1097/MD.0000000000008892
- Wong, J.Y., Carvalho, B., & Riley, E.T. (2013). Intrathecal morphine 100 and 200 µg for post-cesarean delivery analgesia; A trade-off between analgesic efficacy and side effects. *International Journal of Obstetric Anesthesia*, 22(1), 36-41. doi:10.1016/j.ijoa.2012.09.006
- Yaksh, T. & Wallace, M. Opioids, Analgesia, and Pain Management. In: Brunton, L.L., Hilal-Dandan, R., & Knollman, B.C. (2018). *Goodman & Gilman's: The pharmacological*

*basis of therapeutics* (13<sup>th</sup> ed.). McGraw Hill Education: New York, NY. Retrieved from <https://accessmedicine-mhmedical-com.ezproxy.library.und.edu/content.aspx?sectionid=170269577&bookid=2189&jumpsectionID=172477006&Resultclick=2#1149946902>

Appendix A

## Anesthesia Considerations for Intrathecal Narcotic Utilization for a Cesarean Section


Tanner Robberstad, SRNA



### Introduction


- Subarachnoid block (SAB) has been utilized for cesarean section cases for decades
- 2016, US registered 3,945,875 births
  - 32% via cesarean section
- Advantages over general anesthesia include
  - Relatively quick/easy performance with rapid onset
  - Decreased mortality
  - More alert neonate with cozier mother-neonate bonding
  - Better post-operative pain control
- Intrathecal narcotic additive primary agent to provide analgesia
  - ASA only offers up recommendation for use, but no specific
  - Results in highly variable practice routines amongst providers
    - Morphine and fentanyl primary focus of this project

(Joshi et al. 2016, Kolesnikov et al. 2015, Apfelmeyer et al. 2015)




### Case Information

- G2P1, 35 y/o female measuring 37 weeks 4 days
- 114kg, 167 cm, BMI 41
- Elective cesarean section due to malposition of baby
- ASA classification 2



### Pre-operative Evaluation

- Medical Hx: HTN, gestational diabetes, headaches
- Surgical Hx: negative, uncomplicated vaginal delivery with epidural
- Medications: methyldopa, metformin, prenatal vitamins
- Airway evaluation: Mallampati II, TM distance >3, full neck mobility, normal dental exam
- Pre-op VS: BP 135/86, HR 88, RR 20, SpO<sub>2</sub> 94%
- Denied any lower back surgery history, spinal abnormalities, or bleeding disorders



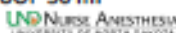
### Anesthetic Course

- Converted for spinal anesthetic with addition of intrathecal narcotic
- Arrived to OR with LR infusing, positioned in sitting position, & prepped in normal sterile fashion
- Subarachnoid space obtained at L3-4 level with 25g, 8.5 inch pencil point Pencil needle
- Injected 0.75% hyperbaric bupivacaine 12mg, fentanyl 10 mcg and duramorph 0.15mg
- Positioned in left uterine tilt and BP monitored every 2.5 minutes
- Complaints of pruritus to face and neck 5 minutes post med injection
- Decreased temperature sensation correlating with T4 dermatome
- Denied feeling abdominal pinch by surgeon with subsequent incision



### Intraoperative Issues

- Uneventful phase
- No drop in BP or feelings of N/V
- Healthy baby delivered with Apgar scores 8/8 at 1 and 5 minutes respectively
- Post placenta delivery
  - 20 units oxytocin in hanging LR liter bag
  - Ondansetron 4 mg, diphenhydramine 12.5 mg, dexamethasone 4 mg, ketorolac 30 mg
- Total 1,200 ml IVF, EBL 700 ml, UOP 50 ml



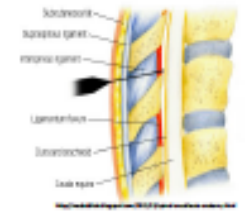
### PACU

- Transported to OB floor in stable condition
- One mild episode of hypoglycemia 73 mg/dL
  - Given apple juice with recheck 142 mg/dL
- Per facility protocol placed on ketorolac 30 mg every 6 hours
- Required no additional opioids during stay
- Discharged home on POD 2

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### Anatomy Review

- Spinal cord terminates at L1 level in adults
- L3 or lower preferred
- Spinal cord meninges
  - Dura mater
  - Arachnoid mater
  - Pia mater
- Spinal ligaments include
  - Supraspinous ligament
  - Interspinous ligament
  - Ligamentum flavum



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### Spinal Anesthesia

- Nerve root principal site of action for SAB
  - Small dose and volume can achieve dense sensory and motor block
  - Sensory blockade associated with posterior nerve roots
  - Motor blockade associated with anterior nerve roots
- Sympathetic nerve fibers exit between T1-L2
  - Blockade results in unopposed parasympathetic activity
    - Results in hypotension

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### Differential Blockade

- Nerves separated into 3 groups
  - A, B, and C fibers
  - A fibers have four subcategories: alpha, beta, gamma, delta
  - Diameter and myelination differentiating characteristics
- Order of blockade progression
  - B > C & A-delta/gamma/beta > A-delta
  - Sympathetic blockade 2-6 dermatomes above sensory block
  - Sensory block 2-3 dermatomes above motor block

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### Intrathecal Analgesia

- 1st pain processing synapses occur in dorsal horn of spinal cord
- Opiate receptor review
  - Mu 1 & 2, kappa, and delta
  - Primarily located in the substantia gelatinosa, laminae II of dorsal horn
- First intrathecal opioid study occurred in 1979 with 2mg morphine
- Able to use significant less medication compared to other routes
- Advantage of prolonging sensory block without affecting motor or sympathetic function & reducing visceral pain

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### Intrathecal Medications

- All should be preservative free agents
- Morphine
  - Hydrophilic > slow onset, prolonged duration
  - Greater cephalocaudal spread > respiratory depression
  - Higher rates of adverse effects (pruritis, N/V)
- Fentanyl
  - Lipophilic > quick onset, short duration
  - Associated with less adverse effects

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### SAB technique

- Pure local anesthetic agent
- Benefit: avoid narcotic side effects
- Disadvantage:
  - Venkata et al. (2015) found ↑ intraoperative hypotension, prolonged period to reach T6 sensory block, reduced postoperative analgesia
  - Onishi et al. (2017) discovered higher doses of 0.5% bupivacaine resulted in a significant increase trend in phenylephrine use and incidence of N/V

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### SAB Technique Cont.

- Morphine additive
  - Highly used adjunct
  - Decreases post-operative pain & improves patient satisfaction
  - Side effect profile creates hesitancy
- Alone or in combination with fentanyl?
  - Sri Salmah & Choy (2009) found morphine superior to fentanyl based on lower post-op visual analogue scores (VAS) & less cumulative morphine PCA use
  - Thornton et al. (2015) found no need for fentanyl as the VAS at 4 hours post-op not significantly different and side effects more common
  - Karaman et al. (2010) also support only a morphine/bupivacaine SAB based on similar block height, time for block onset, similar intraoperative pain scores, and occurrence of side effects

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### SAB Technique Cont.

- Morphine dose
  - Highly variable in practice and numerous research articles investigating
  - Carvalho & Tenorio (2013) found no statistical difference in moderate/severe post-op pain scores between morphine 50 mcg and morphine 100 mcg
  - Wong et al. (2013) in comparison found patients receiving morphine 200 mcg had better post-op analgesia and consumed less rescue opioids when compared to morphine 100mcg
    - However, nausea and anti-emetic use also greater
  - Sultan et al. (2016) found insignificant difference in post-op pain scores between low dose (50-100 mcg) morphine and high dose (>100-250 mcg) morphine
    - HD group had 4.5 hour longer duration before first analgesic request
    - HD also had increased pruritus, N/V, & antiemetic use

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### SAB Technique Cont.

- Morphine & Respiratory Depression
  - Lack of universal definition regarding respiratory depression makes exact incidence difficult to compute
    - Reported as low as 0-0.26%
    - Latha et al. (2017) found significant higher rates however
  - Increasing dose, increases risk
  - Progesterone theoretically combats by stimulating respiratory system, ↑ minute ventilation, ↓ PaCO<sub>2</sub> & causing mild respiratory alkalosis

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### SAB Technique Cont.

- Fentanyl additive
  - Intraoperative and immediate post-op analgesia
  - Weigl et al. (2016) discovered lower intraoperative pain scores and less rescue medication need in the first 12 hours post-op with fentanyl use
    - Pain scores similar between 12-24 hour period
    - Fentanyl 25 mcg can prolong analgesia averaging between 3 to 5 hour post-operatively
    - Doses 10 mcg and greater abolish intraoperative visceral pain in almost all cases

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### SAB Technique Cont.

- Combination of morphine/fentanyl
  - Ideal characteristics with fast onset fentanyl producing intraoperative analgesia and long lasting morphine providing post-op analgesia
  - Side effect rates slightly increased
  - Weigl et al. (2017) found morphine/fentanyl group required less intraoperative opioids, but more than double the amount in the first 1-12 hours post-op
    - Spinal opioid tolerance
    - Receptor availability theory

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### Recommendations

- Intrathecal narcotic utilization for cesarean section is beneficial
- Would recommend against sole fentanyl addition
- Morphine at a dose between 100-150 mcg alone or in combination with fentanyl 10-25 mcg provides adequate analgesia
- Need proper staff education and monitoring protocols when morphine is used
- Thorough discussion with each patient regarding potential benefits and possible adverse effects should be held prior to SAB "cocktail"




### Conclusion

- The use of intrathecal morphine & fentanyl in combination with 0.75% hyperbaric bupivacaine in this case is supported by the literature
  - Patient required no additional narcotics during stay
  - Had one episode of intraoperative pruritus
    - Masked by anti-emetic: "cocktail"?
- Intrathecal narcotics in combination with local anesthetics provide adequate analgesia for cesarean sections which benefits both mother and neonate and should be incorporated into practice by anesthesia providers




### References

1. ... 2. ... 3. ... 4. ... 5. ... 6. ... 7. ... 8. ... 9. ... 10. ... 11. ... 12. ... 13. ... 14. ... 15. ... 16. ... 17. ... 18. ... 19. ... 20. ... 21. ... 22. ... 23. ... 24. ... 25. ... 26. ... 27. ... 28. ... 29. ... 30. ... 31. ... 32. ... 33. ... 34. ... 35. ... 36. ... 37. ... 38. ... 39. ... 40. ... 41. ... 42. ... 43. ... 44. ... 45. ... 46. ... 47. ... 48. ... 49. ... 50. ... 51. ... 52. ... 53. ... 54. ... 55. ... 56. ... 57. ... 58. ... 59. ... 60. ... 61. ... 62. ... 63. ... 64. ... 65. ... 66. ... 67. ... 68. ... 69. ... 70. ... 71. ... 72. ... 73. ... 74. ... 75. ... 76. ... 77. ... 78. ... 79. ... 80. ... 81. ... 82. ... 83. ... 84. ... 85. ... 86. ... 87. ... 88. ... 89. ... 90. ... 91. ... 92. ... 93. ... 94. ... 95. ... 96. ... 97. ... 98. ... 99. ... 100. ...



### References Cont.

101. ... 102. ... 103. ... 104. ... 105. ... 106. ... 107. ... 108. ... 109. ... 110. ... 111. ... 112. ... 113. ... 114. ... 115. ... 116. ... 117. ... 118. ... 119. ... 120. ... 121. ... 122. ... 123. ... 124. ... 125. ... 126. ... 127. ... 128. ... 129. ... 130. ... 131. ... 132. ... 133. ... 134. ... 135. ... 136. ... 137. ... 138. ... 139. ... 140. ... 141. ... 142. ... 143. ... 144. ... 145. ... 146. ... 147. ... 148. ... 149. ... 150. ... 151. ... 152. ... 153. ... 154. ... 155. ... 156. ... 157. ... 158. ... 159. ... 160. ... 161. ... 162. ... 163. ... 164. ... 165. ... 166. ... 167. ... 168. ... 169. ... 170. ... 171. ... 172. ... 173. ... 174. ... 175. ... 176. ... 177. ... 178. ... 179. ... 180. ... 181. ... 182. ... 183. ... 184. ... 185. ... 186. ... 187. ... 188. ... 189. ... 190. ... 191. ... 192. ... 193. ... 194. ... 195. ... 196. ... 197. ... 198. ... 199. ... 200. ...



Thank You  
Are There Any Questions?

