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MINIREVIEWS

# Anaesthesia for patients with arrhythmogenic right ventricular dysplasia

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## Abstract

Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited heart muscle disease. Myocyte apoptosis and fibro-fatty scar tissue predisposes patients to malignant ventricular arrhythmias. Patients may present to variety of surgical procedures with diagnosed ARVD. Surgical insult, catecholamine surge and physiological disturbance can be hazardous on the vulnerable myocardium and may result in life-threatening ventricular tachycardia or sudden cardiac death in the perioperative period. Anaesthetists have particular role in perioperative management of this patient population, meticulous perioperative planning, close haemodynamic monitoring and maintenance of physiological stability throughout helps to avoid devastating perioperative loss.

**Key words:** Arrhythmogenic right ventricular dysplasia; Arrhytmogenic cardiomyopathy; Anaesthesia



**Core tip:** Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited disease of the cardiac muscle, characterised by progressive myocyte death and scarring of the myocardium associated with ventricular tachycardia and sudden cardiac death. Electrical instability is exacerbated by physiological changes induced by surgical insult and may lead to unexpected perioperative death. Careful anaesthetic management can minimise stress response and reduce the incidence of malignant ventricular arrhythmias in the perioperative period. In this article we discuss the available literature with the aim to provide some guidance for the clinical anaesthetist encountering patient with ARVD.

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## INTRODUCTION

Arrhythmogenic right ventricular dysplasia (ARVD) is inherited cardiomyopathy characterised by progressive

death of the myocytes most commonly in the right ventricle. Fibro-fatty replacement of the myocardium forms scar tissue causes malignant ventricular arrhythmias, sudden cardiac death (SDC), or cardiac failure. In the late stages it affects both left and right ventricles. Early diagnosis could offer control over progress of the disease and prevention of malignant arrhythmias and cardiac arrest. Once arrhythmia control is achieved AVRD could become a stable condition[1,2].

Patients with ARVD undergo variety of surgical procedures in their life span. This is why the condition is of a particular interest for anaesthetists and perioperative physicians. Physiological changes and medication in the perioperative period may have proarrhytmogenic effect. Surgical insult activates stress response with catecholamine surge while adverse effects of anaesthetic agents induce significant cardiovascular instability.

AVRD have autosomal dominant inheritance pattern with an estimated prevalence rate of 1:5000 that may be underestimated. Forensic autopsy following unexpected perioperative death in young individuals proved ARVD in eighteen out of fifty patients[3]. It is common enough for most anaesthetists to encounter a patient with ARVD at some point in their career either: (1) In the subclinical stage, leading to sudden perioperative death in seemingly healthy patients undergoing low-risk surgical intervention. In such cases post mortem examination could confirm the diagnosis of ARVD; or (2) in patients with established diagnosis of ARVD presenting for elective or emergency surgical procedure. Disease may be in the early or advanced stage at the time of presentation, symptoms may be well or poorly controlled.

Literature on the management of ARVD in the anaesthetic practice is based on a small number of individual case reports describing anaesthetic technique used in patients with subclinical or diagnosed ARVD. Straightforward link between anaesthetic agents and perioperative mortality is difficulty to establish. Previously uneventful general or regional anaesthesia does not exclude ARVD. It could be that perioperative death is associated with physiological instability, rather than administration individual anaesthetic agent. Majority of the recommendations on perioperative management of these patients are based on case reports when many things have gone wrong, and it is difficult to untangle whether a particular medication was a culprit. Not many anaesthetists have had frequent exposure to ARVD patients to be able to scientifically approach the management. In this review we will discuss the literature on presentation and perioperative management of these patients, and add some of the experience of our centre where there is an unusually high concentration of ends stage cardiac failure ARVD patients.

## PATHOGENESIS AND GENETICS

ARVD in an heritable cardiac muscle disease, most commonly follows autosomal dominant inheritance with variable penetrance in families and wide spectrum of disease severity[4]. AVRD does not present at birth. Symptoms develop in adolescence, and diagnosis is commonly made in the second and third decade of life. ARVD affects young men three times more frequently than women and an important cause of SCD in young adults and athletes[5-7].

ARVD incidence remains unclear, prevalence is estimated between 1 in 2000-5000 showing high variability between geographical regions. Positive family history presents in up to 50% of the cases. High incidence was observed in Vento region of Italy where forensic autopsy proved ARVD behind SCD in 20% of the cases[8,9]. Autosomal recessive forms are less common, Naxos disease is associated with palmoplantar keratosis and severe cardiac features[10].

AVRD develops due to desmosomal and non-desmosomal gene mutation. Gene mutation alters protein synthesis. Desmosomes (also called macula densa) are the structural and functional units of the heart muscle cell, connecting cells in the intercalate discs and mediating intracellular signal conduction. Disrupted desmosomal structure cannot withstand physical activity and shear forces and induces cardiomyocyte death. Apoptotic cells are replaced with fibro-fatty tissue causing increased excitability and structural abnormality. Initially focal process becomes generalised leaving extensive scar tissue with scattered residual myocytes within the thin ventricular wall. Gene mutation alters the structure of the following five desmosomal proteins: Plakoglobin, Desmoplakin, Plakophillin, Desmoglein and Desmocollin.

Non-desmosomal gene mutations are also found to be linked to AVRD. Ryanodine receptor-2 mutation causes ryanodine receptor dysfunction and alter intracellular calcium release from the sarcoplasmatic reticulum. Transforming growth factor-B3 gene mutation may have a role in myocardial fibrosis whilst *TMEM43* gene mutation may cause dysregulation in adipogenic pathway and induces fibro-fatty replacement of the cardiomyocytes[2,11,12].

## DIAGNOSIS

AVRD is difficult to diagnose when asymptomatic. First presentation is cardiac arrest in up to 50% of the clinical cases. Post mortem examination confirms fibro-fatty histology. Screening of family members is important to identify and risk stratify genetically affected relatives to prevent SDC.

Diagnostic test specific for ARVD has not been invented. In 1994, the International Task Force proposed the first diagnostic criteria system and combined multiple diagnostic information (structural, histological, arrhythmic, echocardiographic, genetic and familiar features). This system highly specific but failed to identify early, asymptomatic and familiar cases. International Task Force Criteria has been modified in 2010. Diagnosis was based on the combination of major and

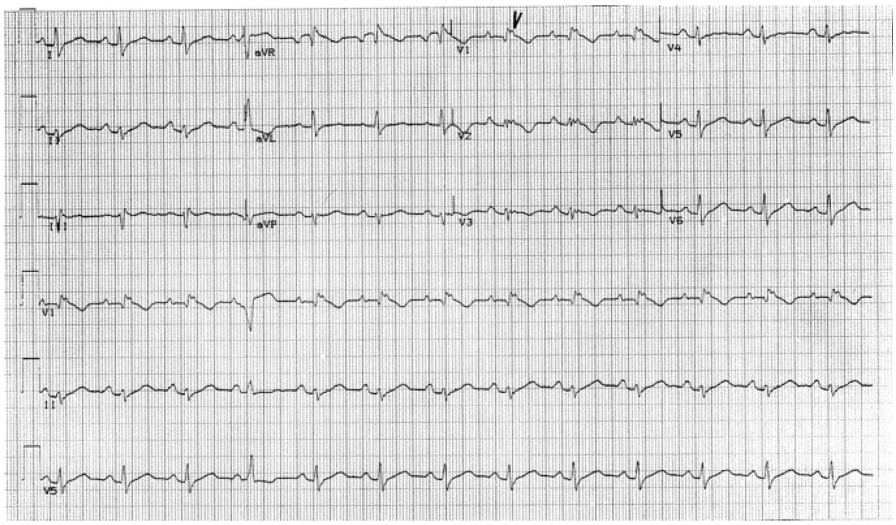


**Figure 1 Twelve-lead electrocardiogram leads with regular sinus rhythm and an epsilon waves (arrow) in leads V1-V3.**

minor criteria[13].

Electrocardiogram (ECG) abnormalities observed include T-wave inversion in anterior precordial leads, left axis deviation, wide QRS complexes and epsilon waves. Ventricular tachy-arrhythmias may present in a wide spectrum on resting ECG from premature ventricular extrasystoles, non-sustained ventricular tachycardia and monomorphic ventricular tachyarrhythmia with left bundle branch block.

Echocardiography may detect regional or global dysfunction, predominantly affecting the RV. RV wall thinning and dilation with tricuspid regurgitation are the features of advanced right heart failure.

Cardiac magnetic resonance imaging (MRI) is a non-specific diagnostic modality, however allows reliable quantification of the right ventricle volume however may fail to detect the ventricular adipose tissue and wall thinning accurately.

Right ventricular angiogram is considered a reliable invasive method for evaluating regional right ventricular wall motional abnormality. Cardiac MRI and 3D Echo-cardiography are non-invasive and preferred over right ventricular angiography for assessing morphology and functional abnormalities of the right ventricle[14].

Ventricular biopsy may confirm the suspected diagnosis of ARVD however negative biopsy should be interpreted with caution. Myocardial sample may be unreliable as AVRD often does not involve the subendocardium whilst the myocardium exhibits patchy involvement. Negative biopsy does not exclude the diagnosis of ARVD[15]. Involvement of a specialist pathologist experienced in this condition is important.

Immunohistochemical analysis: Reference diagnostic test highly sensitive and specific to ARVD would provide accurate early diagnosis in asymptomatic cases. Immunohistochemical analysis of plakoglobin in the intercalate discs found reduced signal level in patients with ARVD and may be of value in diagnosing ARVD[16,17] (Figure 1).

## TREATMENT

Current data suggest that asymptomatic patients with established ARVD do not benefit from prophylactic therapeutic interventions.

Once the clinical diagnosis of ARVD is established, treatment modalities target three main goals.

### *Life-style modification*

Clinical evidence suggests the strenuous physical exercise accelerates myocyte apoptosis and increase the risk of SDC in competitive athletes. Physical exercise may also be responsible for "hot disease phase" when myocyte atrophy accelerates. This phase is characterised by increased excitability[18,19]. Restriction from strenuous exercise and competitive sports is thought to be slow down myocardial cell death.

### *Prevention or effective termination of recurrent arrhythmias*

Ventricular arrhythmias manifest in a wide spectrum. Sporadic premature ventricular extrasystole may progress to non-sustained or sustained ventricular tachycardia and VF. VF leads to sudden cardiac arrest. Long term arrhythmia control may be achieved with implantable cardioverter defibrillator (ICD) alone or in combination with antiarrhythmic drugs.

The effect of β-blockers or Amiodarone in treatment of sustained VT has been proven. Sotalol provides the most effective arrhythmia control. Amiodarone is usually preserved for advance heart failure. In combination with B-blocker its efficacy is comparable to Sotalol[20,21].

ICD is considered for primary prevention in high risk cases and proved to be successful when cardiac dysfunction occurs. However ICD for AVRD treatment will require long term follow up and may be complicated with adverse effects associated with procedures. When cardiac failure is a problem the ICD can be also used as a biventricular re-synchronisation therapy too[22].

Catheter ablation: Developing fibro-fatty scar tissue with scattered myocytes increases the risk of re-entrant tachycardia. Catheter ablation is reserved for patients with recurrent ventricular arrhythmia not responsive to pharmacological treatment as it only offers short-term success, long-term efficacy remained debatable[23].

### *Cardiac failure*

Symptomatic heart failure is rare and occurs predominantly in advanced stage. Cardiac failure should be treated in conjunction with conventional heart failure guidelines, most commonly with angiotensin-converting enzyme inhibitors, diuretics, digoxin and anticoagulants. In the rare occasions, when heart failure is unresponsive to medical management, heart transplantation may be necessary.

## ANAESTHETIC CONSIDERATIONS

Given a prevalence rate of 1:5000, most anaesthetists will encounter a patient with ARVD during their practice. SDC during general anaesthesia is unresponsive to cardiopulmonary resuscitation. Disease awareness, understanding pathophysiology and hazardous conditions help improve safety in these patients. Perioperative management is divided in two groups: For patients with already diagnosed ARVD, and for patients who present with malignant arrhythmias and SDC.

### *Preoperative management*

Preoperative evaluation of patients with AVRD should include collecting medical history, documenting physical findings and obtaining specialized diagnostic tests. All elective patients must be consulted with a cardiologist with experience with the disease. History of provoked arrhythmias and safe medication is essential.

Subclinical stage of ARVD is symptomless or characterised by non-specific clinical symptoms such as palpitation, chest pain and syncope. Linking these features to a rare cardiac muscle disease may be difficult. Previous uneventful general or regional anaesthesia does not exclude ARVD[24]. ECG is not used for routine assessment in young and healthy patients.

Patient with confirmed diagnosis of ARVD should undergo regular follow up to evaluate efficacy of arrhythmia control and cardiac function. Review of case notes and discussion with a cardiologist would enable the anaesthetist to gain information about the course of the disease. Physical examination carries limited significance in early stages, signs and symptoms of systemic or pulmonary congestion become apparent in advanced stage. Twenty-four hour holter-monitor is a reliable non-invasive method to discover sustained and non-sustained ventricular tachycardia. Echocardiography is available in most institutions to offer a quick insight to cardiac function. Preoperative optimisation carries high impact on perioperative mortality. Multidisciplinary team approach including cardiologist, anaesthetist and operating surgeon facilitate safe perioperative planning. Elective procedure should be postponed until ventricular arrhythmia controlled and heart failure is optimised. Regular anti-arrhytmic drugs should be continued until surgery. Patient with ICD should undergo device check to assess optimal function and number of appropriate ICD discharges. Electrical safety may warrant inactivation of the device in the immediate preoperative period[25].

### *Intraoperative management*

Maintaining haemodynamic state near to the normal physiological conditions is likely to offer best arrhythmia protection. Close haemodynamic monitoring is essential for early recognition of physiological instability and assessment cardiovascular response to intervention. Routine monitoring with ECG, oxygen saturation probe, non-invasive blood pressure cuff and capnography may be supplemented with invasive arterial blood pressure cannula even in case of minor surgical procedures. Invasive arterial pressure monitoring will allow for blood pressure monitoring even in the face of arrhythmia, when NIBP could be unreliable. Major interventions warrant more invasive monitoring. Central venous pressure provides information about right heart function and filling status. The role of pulmonary artery catheters may be controversial outside specialised cardiothoracic institutions due to induction of malignant ventricular arrhythmia and ventricular perforation during placement. However, intraoperative transoesophageal echocardiography offers superior diagnostic and avoids risks of arrhythmia. Less invasive forms of continuous cardiac output monitoring allow assessment of contractility, ventricular filling.

Malignant ventricular arrhythmia and SCD could occur at induction of general anaesthesia, during the surgical procedure or in the immediate postoperative stage. Therefore, appropriate post-operative monitoring and care locations must be chosen according to institutional organisation.

### *Safe anaesthetic management is facilitated by the following two principles*

**Understanding the pharmacokinetics and adverse effects of the anaesthetic agents:** Hemodynamic variation during anaesthesia is related to specific effects of the anaesthetic agents on the sympathetic nervous system. Patient with extensive sympathetic blockade are prone to develop reduced systemic vascular resistance, reduced cardiac output and severe arterial hypotension.

Midazolam causes little direct myocardial depression and was reported to be safe for sedation in conjunction with opioid analgesics or for induction of general anaesthesia in combination with a different induction agent[26]. However in two case reports administration of Midazolam was associated with perioperative death[27,28]. Propofol is known to induce significant arterial hypotension and myocardial suppression. Judicious dosing or slow infusion for induction may help to overcome these

unfavourable pharmacological properties making it one of the commonly used induction agent. Maintenance of general anaesthesia using Propofol gains increasing popularity. Case reports describe Propofol as a safe agent for induction[27] and maintenance of general anaesthesia[26]. Ketamine has a stable haemodynamic profile however anticholinergic effect can result in sinus tachycardia.

Opioid analgesia should be selected carefully. Perioperative death in patients with diagnosed ARVD was reported after administration of Sufentanyl[28]. Fentanyl is considered to be safe[28,29]. High dose of Fentanyl was used in a cardiothoracic patient population[26].

Volatile anaesthetic agents should be administered cautiously to patients with ARVD as these are known to induce dose-dependent myocardial depression, tachycardia and arterial hypertension. Isoflurane was associated with intraoperative SCD but paradoxically, uneventful anaesthesia was also described[27-31].

Muscle relaxants have several unfavourable side effects on the circulation. Careful selection helps to avoid haemodynamic instability. Perioperative death was observed in a patient receiving Suxamethonium and Atracurium[32]. This had been explained by histamine release followed haemodynamic instability. Cisatracurium has minimal effect on the cardiovascular system and was associated with positive patient outcome[31]. Pancuronium is likely to induce sinus tachycardia due to its vagolytic effect and thought to be contraindicated in patients with ARVD. However Pancuronium was the muscle relaxant of choice in successful case series of intraoperative management of patients with advance cardiac failure ARVD patients undergoing orthotopic cardiac transplantation. There were no deleterious effects reported[26,33].

Anticipating and promptly responding physiological disturbance. These are the principles of balanced anaesthesia for all operations. However, there are no more important in any other group of patients other than ARVD.

### *Arterial perfusion pressure*

Hypertension increase afterload on the diseased ventricle. Hypertension may be treated with deepening the plane of anaesthesia. Intravenous Nicardipine has been described as a safe choice. Although there is lack of experience, it is possible that other systemic blood pressure lowering agents are safe too.

Hypotension could diminish coronary perfusion and oxygen delivery. Although direct vasoactive drugs can provoke arrhythmias, these may need to be used to maintain haemodynamic parameters. Vasopressor infusions have been previously described. Dopamine is known to increase the incidence arrhythmias whilst used to treat arterial hypotension[34], however safe administration in patients with ARVD was reported in the literature[26].

### *Heart rate and rhythm*

Tachycardia increases the incidence of premature ventricular complexes and ventricular extrasystole predisposing to malignant arrhythmias. During general anaesthesia tachycardia may be explained by for several factors. Pain control, adequate depth of anaesthesia and muscle relaxation should be maintained at all time. Agents with positive dromotropic and batmotropic effects have to be avoided where possible. Controlling electrolyte levels of potassium and magnesium can offer some protection. Persistent tachycardia may be treated with short acting intravenous β-blocker (Esmolol). When premature ventricular extrasystole increases in number, Amiodarone infusion should be commenced.

### *Volume status*

Excessive intravenous fluid administration is hazardous in case of ventricular dysfunction as it can distend the heart. Hypovolaemia secondary to dehydration or large fluid shift during complex abdominal and thoracic procedures should be treated intravenous crystalloid. Anticipating and promptly responding to haemorrhage helps to avoid decompensated blood. Compensatory tachycardia to maintain cardiac out and oxygen delivery predisposes to malignant tachyarrhythmia.

### *Normoxia and normocapnia*

Controlled ventilation maintains normal arterial carbon-dioxide partial pressure ($pCO_2$). Tachycardia may be the first manifestation of increased $pCO_2$. Muscle relaxation in major surgical cases could offer also reduction of oxygen demand due to reduced striated muscle oxygen demand.

### *Normothermia*

Hypothermia increases the risk of shivering and increased oxygen consumption and predispose to tachyarrhythmia.

### *Electrolyte and acid-base balance*

Calcium, magnesium and potassium play important role in regulation of cardiac function and vessel tone. Deranged plasma level can precipitate haemodynamic instability. Metabolic acidosis has deleterious effect on cardiac contractility and reduces sensitivity to endogenous and exogenous catecholamines.

### *Postoperative care*

Postoperative care plays an important role, malignant arrhythmia in the postoperative phase must be anticipated and predisposing factors prevented or promptly eliminated. ARVD may present exclusion criteria for day surgery even following low risk surgical interventions. Patient with ARVD should be cared for in a clinical area where close monitoring can be maintained.

Maintaining physiological parameters near to the normal values decreases the incidence of malignant arrhythmias and SDC.

**Table 1 Anaesthetic management of patients with arrhythmogenic right ventricular dysplasia**

| | |
|---|---|
| Preoperative management | |
| History | Symptomatic arrhythmia, cardiac drug history, cardiology follow-up |
| Physical findings | Signs of systemic and pulmonary congestion |
| Specific diagnostic tests | ECG, Holter monitor, Echocardiography |
| Preoperative optimisation | Multidisciplinary approach involving cardiologist, surgeons, anaesthetists and intensivists |
| Intraoperative management | |
| Monitoring | Minor surgical intervention: ECG, non-invasive blood pressure monitoring, $SpO_2$, capnography<br>Major surgical interventions: Central venous pressure, pulmonary artery catheter and cardiac output monitoring, temperature monitoring, intraoperative transoesophageal echocardiography |
| Haemodynamic stability | Maintaining adequate depth of anaesthesia and analgesia<br>Adequate arterial perfusion pressure<br>Avoiding tachycardia, bradycardia and arrhythmias<br>Avoiding blood loss, hypovolaemia and fluid overload<br>Maintaining adequate gas exchange<br>Temperature control<br>Electrolyte balance<br>Acid-base balance |
| Choice of anaesthetic agents and vasoactive drugs | Understanding pharmacokinetics and side effects of the individual anaesthetic agents and anticipating cardiovascular effects |
| Postoperative management | Cardiovascular stability: Avoiding hypo- and hypertension, tachycardia, bradycardia and arrhythmias<br>Prompt recognition of blood loss and hypovolaemia<br>Normoxia and normocapnia<br>Temperature control<br>Adequate pain control<br>Early treatment of postoperative nausea and vomiting<br>Electrolyte and acid-base balance |

ECG: Electrocardiogram.

Adequate arterial perfusion pressure is essential to maintain coronary perfusion pressure, myocardial oxygen supply and end-organ perfusion. Perioperative clinicians should have low threshold to treat bradycardia and tachycardia. Close monitoring of fluid balance and early recognition of significant aim to maintain haemodynamic stability.

Supplemental oxygen may help to avoid arrhythmias induced by hypoxia, however, importance of adequate carbon-dioxide removal must not be overlooked.

Adequate pain control reduces anxiety, maintains autonomic stability and prevents further catecholamine surge. Multimodal approach with non-opioid analgesic drugs may be appropriate choice after minor surgical interventions. Opioids analgesics have significant side effects on the cardiovascular and respiratory systems and their use is reserved to treat severe postoperative pain after. Regional and neuroaxial blockade may be useful after major surgical interventions.

Satisfactory treatment of postoperative nausea and vomiting eliminates vagotonic effect. Electrolyte balance maintains electrical stability of the diseased myocardium.

When malignant supraventricular or ventricular arrhythmia occurs, pharmacological treatment or electrical cardioversion should not be delayed. Prompt consideration of reversible causes and electrolyte abnormalities may help to restore cardiovascular stability. Early involvement of experienced cardiologist should be thought. Management of cardiovascular collapse follows Adult Life Support (ALS) guidelines (Table 1).

## SPECIAL FIELDS OF ANAESTHESIA

### *Obstetric anaesthesia*

In pregnancy all maternal organ system undergoes physiological changes in order to adapt to increased metabolic demand of the foetus and prepare the maternal body for delivery. Cardiovascular changes occur throughout pregnancy: Systemic vascular resistance decreases initially due to progesterone effect and low resistance placental vascular bed later on. Cardiac output may increase up to 50% at term due to left ventricular hypertrophy. Intravascular volume expansion induces physiological anaemia. Healthy gravidas tolerate adaptation well, women with structural heart disease may experience worsening symptoms while pregnant.

Limited available data describes pregnancy safe and well-tolerated in women with mild to moderate form of ARVD, however all women with ARVD in child-bearing age should receive counselling before pregnancy.

In an ideal world all pregnant women with ARVD should be assessed by multidisciplinary team including specialist cardiologist, obstetrician and anaesthetist as soon as pregnancy discovered. Early assessment enables the medical team to plan essential investigation, maintain effective control of malignant arrhythmias and establish a robust plan for delivery and the postpartum period.

Anaesthetists are likely to encounter the following issues whilst managing pregnant women with AVRD: (1)

discontinuation of pharmacological control of malignant arrhythmias: Omission of regular antiarrhytmic drugs have been reported with minimal effect[35]; (2) amiodarone is associated with severe adverse effect on the foetus therefor it needs to be used only to treat life-treating arrhythmias. β-blockers may be associated with intra-uterine growth retardation however Bisoprolol is considered to be safe[36]; (3) alteration of heart failure medications due to their teratogenic effect: While Warfarin and ACE-inhibitors may be associated with faulty foetal organogenesis, most diuretics, digoxin and low molecule weight heparin can be used without having an adverse effect on the foetus[36,37]; and (4) worsening cardiac function and symptomatic ventricular arrhythmia: Despite of continuous rhythm control, women may experience increased incidence of palpitation. Evaluation of cardiac function with echocardiograph and holter monitor is described to be beneficial.

### *Labour and delivery*

ARVD is not a contraindication of vaginal delivery, however significant deterioration of pre-existing heart failure might indicate surgical delivery. Planned delivery may provide a better control of perinatal events.

In labour cardiac output increases 85% above the non-pregnant level. This is due to increased venous return from the placental vessels with each uterine contraction. Furthermore, anxiety and pain results in sympathetic stimulation and increase heartrate. Low dose spinal or effective epidural anaesthesia achieves good pain relief and blunts autonomic response but also warrants higher level of haemodynamic monitoring to avoid cardiovascular instability.

Successful surgical delivery of healthy new born has been described both under regional and general anaesthesia[35,36,38]. Suitable technique is determined by maternal choice and the degree of heart failure. There is no evidence to supports one technique over the other. The ultimate goal is to maintain cardiovascular stability. Haemodynamic instability is more common with spinal anaesthesia, epidural anaesthesia allows better control over instability and more time for adaptation.

Most commonly used oxytocin has deleterious side effects such as hypotension and tachycardia, dilution and slow administration may overcome. It is important to judge whether use of oxytocin is needed for the individual ARVD patient at all, rather than follow the routine protocol for all patients. Involvement of experienced obstetrician in these cases is important.

### *Postnatal period*

Increased incidence of malignant arrhythmias has been reported in the third trimester and the postpartum period. High level of monitoring is recommended in the early postpartum phase. Lactation raises concern about electrolyte derangement however there is no report of ventricular tachyarrhythmia in women who opted for breast feeding. Evaluation of cardiac function 3 mo after delivery provides good guide regarding the need for modifying pharmacological arrhythmia control.

### *Regional anaesthesia*

Local anaesthetic drugs exert effect by blocking voltage sensitive sodium channels and inhibit propagation of action potential *via* the nerve fibres.

Regional blocks may provide anaesthesia as a sole technique or used as an adjunct to general anaesthesia to facilitate adequate analgesia and blunt stress response to pain.

Cardiovascular changes are the most important effects of central neural block. These responses are due to arterial vasodilation and decreased contractility due to sympathetic denervation. Reflex tachycardia aims to maintain cardiac output however significant decrease in systemic vascular resistance due to sympathectomy reduces venous return and paradoxically induces bradycardia or asystole.

Anaesthetists should anticipate these changes when planning central neuraxial blockade for a patient with ARVD. Remembering of non-specific symptoms such as nausea, vomiting and syncope may be helpful to avoid cardiovascular collapse.

Epidural anaesthesia provides better controlled onset of the blockade with less marked effect on cardiovascular system. However, it also uses large doses of local anaesthetics, which can cause arrhythmias after their systemic absorption.

Local anaesthetics exhibit dose dependent sodium channel blockage on the cardiac muscle, inducing prolongation of the PR interval and widening the QRS complexes. Direct cardiac toxicity depends on the potency. Bupivacaine is the most commonly used local anaesthetic agent however its higher plasma level is associated with severe adverse effect on the cardiovascular system.

There is no sufficient data to support any local anaesthetic agent being superior to other, Bupivacaine was associated with perioperative death in patients with ARVD and used successfully during surgical delivery[29,38]. In fact, it may support the concept that perioperative death is associated with deleterious haemodynamic instability rather than the choice of the local anaesthetic agent.

Ephedrine is frequently administered concomitantly with local anaesthetic drugs with the aim to prevent rapid absorption to the circulation and avoid toxic plasma level. It also increases the duration of the blockade. Subcutaneous and extravascular administration is associated with minimal cardiovascular sequels. Intravascular use could induce hypertension, tachycardia and increased myocardial oxygen consumption predisposing patients with ARVD to malignant ventricular arrhythmias and SDC.

### *Laparoscopic surgery*

Laparoscopic surgery an important diagnostic and

therapeutic tool and gaining increased popularity over the past two decades. Growing surgical experience and better understanding of the physiological effect of pneumoperitoneum lead to that more and more major surgical interventions are being performed laparoscopically.

Laparoscopy offers lower perioperative morbidity, better wound healing, fewer wound infection and better pain control allowing early mobilisation and shorter hospital stay.

Anaesthetists should be aware of the physiological changes induced by laparoscopic surgery whilst preparing a patient with diagnosed ARVD for surgery: Mechanical effect of pneumoperitoneum has significant cardiovascular consequences: Reduced venous return due to compression of the inferior vena cava, increased myocardial afterload and bradycardia secondary to increased systemic vascular resistance. Compensatory tachycardia precipitates malignant arrhythmias. Carbon-dioxide insufflation may induce respiratory acidosis. Perforation of the solid organs or great vessels precipitates decompensated blood loss.

Laparoscopy does not have absolute contraindications, however patients with diagnosed ARVD or advanced heart disease need to be assessed on an individual basis. Operative planning should involve surgeon, anaesthetist and specialist cardiologist. Experienced surgeon can reduce intraoperative complication and the duration of the surgical intervention. Anaesthetist should anticipate and respond to cardiovascular changes. Invasive haemodynamic monitoring may be necessary for minor procedures. Postoperative nausea and vomiting are common, prevention with combined antiemetic drugs is recommended. Persisting haemodynamic concerns should prompt early discussion with the operating surgeon and conversion to open procedure should be thought.

## MANAGEMENT OF PERIOPERATIVE CARDIOVASCULAR COLLAPSE IN PATIENTS WITH SUSPECTED ARVD

Undiagnosed ARVD often presents as unexpected perioperative death in young and fit patient undergoing minor surgical intervention. Cardiovascular collapse is commonly unresponsive to cardiopulmonary resuscitation.

It such cases all anaesthetists ask for help, and it is the culture of perioperative case. Once cardiovascular collapse occurs, management should follow the ALS guidelines. Defibrillation is almost always needed. Administration of Amiodarone bolus and infusion should follow ALS guidelines. Other reversible causes should be considered, intravascular volume, electrolytes should be replaced.

Patent airway and controlled ventilation aim to maintain adequate arterial oxygen and carbon-dioxide pressure and avoid arrhythmia induced by hypoxia and hypercarbia.

## PRACTICAL CONSIDERATIONS

AVRD is a rare form of cardiomyopathy, subclinical stage may be asymptomatic or characterised by non-specific symptoms such as palpitation or chest pain. Awareness amongst anaesthetists may help to raise the suspicion. When malignant tachycardia occurs is healthy individual in the perioperative period, differential diagnosis should include ARVD. Early recognition and prompt treatment of these arrhythmias may help to avoid cardiovascular collapse.

Patients with established diagnosis of ARVD should be managed by a multidisciplinary team. Robust perioperative plan should include preoperative workup and optimisation involving a cardiologist. Surgical intervention must be performed by an experienced consultant surgeon with the least haemostatic disturbance. Experienced consultant anaesthetist in charge for the anaesthetic management should understand the pathophysiology of ARVD and physiological anomalies predisposing to adverse events. Cardiovascular stability should be maintained throughout. Malignant arrhythmias and cardiovascular collapse can occur at any time during the perioperative care therefor emergency vasoactive and anti-arrhythmia drugs and defibrillator should be available. Postoperative recovery is the best to take place in a clinical area with high level of monitoring. Stable haemodynamic parameters, adequate analgesia and temperature control, fluid and electrolyte balance aim to avoid arrhythmias and facilitate early recovery, mobilisation and hospital discharge. Once adverse event occurs at any point during perioperative care, experience cardiologist can offer valuable input.

## CONCLUSION

Most anaesthetists would encounter patients with subclinical or diagnosed ARVD. Available literature on management of ARVD in the anaesthetic practice is not sufficient to establish evidence-based recommendations. Clinical data remains conflicting about the safety of the individual pharmacological agents. Careful perioperative assessment and solid management plan focusing on the maintenance of physiological stability may help to avoid perioperative loss and provide the highest level of safety in this patient population.

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MINIREVIEWS

# Anesthetic considerations for liver diseases unique to pregnancy

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## Abstract

Liver diseases that are most unique to pregnancy consist of hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hemolysis, elevated liver enzymes and low platelets syndrome. In this review, risk factors, etiology, symptoms, diagnosis, prognosis and treatment of each entity followed by principles of anesthetic management based on the case reports or retrospective records will be addressed.

**Key words:** Liver disease; Pregnancy; Anesthesia



**Core tip:** Liver diseases like hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy and hemolysis, elevated liver enzymes and low platelets are challenging for anesthesiologists because of the increased risk of morbidity and mortality. Therefore, general and specific anesthetic management strategies are of utmost important. In this review, the risk factors, etiology, symptoms, diagnosis, prognosis and treatment of these liver diseases during pregnancy and general principles of anesthetic management based on our case report and retrospective records will be addressed.

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## INTRODUCTION

Most unique liver diseases that occur during pregnancy are hyperemesis gravidarum (HG), acute fatty liver of pregnancy (AFLP), intrahepatic cholestasis of pregnancy (IHCP), and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome[1,2]. We aim to present risk factors, etiology, symptoms, diagnosis, and prognosis briefly and as well as discuss the treatment of each

entity, principles of anesthetic management based on the current literature.

## HG

HG, generally occurs generally at 4-10 wk of gestation up to 20 weeks' gestation[3-5]. There are risk factors such as history of HG, hyperthyroidism, psychiatric illness, molar pregnancy, preexisting diabetes, multiple gestations, multiparity, increased body mass index, and excessive daily intake of saturated fat before pregnancy are some of the common risk factors[1]. Female fetus and maternal *Helicobacter pylori* infection might be considered as additional risk factors[6]. The incidence, etiology, symptoms, diagnosis and treatment of the disease were summarized in Table 1[5,7-17].

We would like to underline our established therapeutic plan based on a 21-year-old woman (G1, P0) with a diagnosed HG without remarkable medical history. She was admitted to our unit at 19[1] weeks' gestation. She was suffering from nausea, vomiting and weight loss refractory to medical treatment though she was treated in another hospital before admission. Her current weight was 56 kg (Pre-pregnancy weight 73 kg), and BMI was 18.3 kg/m$^2$. Her vital signs including blood pressure and heart rate were 90/60 mmHg and 90 beat/min, respectively. Blood and urine laboratory results and thyroid function tests were within normal clinical limits. Obstetric and abdominal USG were unremarkable. Medical treatment was started with metochlopramide and vitamin B during IV total parenteral nutrition. Fluid intake and urine output were adjusted accordingly. Because of persistent refractory nausea and vomiting, metoclopramide was switched to domperidon. For differential diagnosis, endoscopy was planned but 1$^{st}$ endoscopy attempt without sedation was unsuccessful. Therefore, 2$^{nd}$ endoscopy was planned using propofol under monitored anesthesia care (MAC). The endoscopy revealed minimal superficial gastritis and motility dysfunction (with no pyloric stenosis and helicobacteria presence). Although there was rarely need for anesthesia in HG since that disease usually seen during early pregnancy period, we performed sedation with propofol which was a safe intravenous anesthetic agent in liver diseases under MAC.

## AFLP

The AFLP is observed 1 in 10000-15000 pregnancies[18]. It often develops between 27-40 weeks' gestation, but may be undiagnosed until the postpartum period[1].

Advanced maternal age, primiparity, multiple pregnancies, preeclampsia, male fetus, being underweight, the use of non-steroidal anti-inflammatory drugs and previous AFLP are considered to be some of the risk factors[1,19]. The incidence of AFLP is high in women with a genetic mutation. Basically, mitochondrial fatty acid oxidation pathway is affected. Fetus has a long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency[7,20]. The incidence, etiology, symptoms, diagnosis and treatment of AFLP were shown in Table 1[7,18,20-29].

Primary obstetric management is to make immediate delivery decision since recovery before delivery is not possible. The anesthesia technique either regional or general must be discussed. General anesthesia is required in patients with coagulopathy because of the concern for regional anesthesia related hematoma risk[1]. Most of the patients recover within 48-72 h after delivery with improved aminotransferase levels[22]. However, patients with coagulopathy, encephalopathy, or hypoglycemia require intensive care admission[26].

Perioperative care includes establishing adequate intravenous accesses readily available for cross-matched blood and blood products against increased risk of postpartum hemorrhage (PPH)[28].

Clinical and laboratory findings, anesthetic managements with maternal and neonatal outcomes of 28 cases from Shanghai Public Health Center were retrospectively reviewed over 5 years. Cesarean delivery was performed under either neuraxial ($n$ = 16) or general anesthesia ($n$ = 12) with rapid sequence induction (RSI). Two maternal deaths (7.1%) without fetal deaths were recorded. As a result of this retrospective study, recommendation of general anesthesia with RSI in case of severe coagulopathy was reconfirmed[29].

## IHCP

The incidence of IHCP is approximately 1-2 in 1000 pregnancies. Generally it manifests either in the second or third trimester, around 30 weeks' gestation. After delivery, symptoms generally resolve[30]. According to the recent reports, the incidence varies between 1.5%-4%[1].

Accused common risk factors are advanced maternal age, multiparity, family history, preexisting liver disease, or history of cholestasis while taking oral contraceptives[31,32].

The incidence, etiology, symptoms, diagnosis and treatment of IHCP were also shown in Table 1[1,30-51].

Diagnosis is based on clinical signs and laboratory tests. Elevated bilirubin levels (< 6 mg/dL), and elevated transaminases (approximately 20 times than normal values). The most sensitive diagnostic biomarker is the elevation in the fasting serum bile acid level. Parturients generally have bile acid levels higher than 10 μmol/L. The degree of disease as mild, moderate or severe is made according to bile acid levels (Mild: 10-39 μmol/mL, moderate: 40-99 μmol/mL and severe: ⩾ 100 μmol/mL)[38].

We have retrospectively documented maternal, fetal and neonatal outcomes of parturients with IHCP delivered in Gazi University. Maternal outcomes were generally good as indicated in many previous reports[28,37,47,48]. Twenty-seven percent of our cases had normal spontaneous vaginal delivery, while the rest (73%) underwent cesarean delivery. Approximately

**Table 1 The incidence, etiology, symptoms, diagnosis and treatment of the liver disease unique to pregnancy**

| Disease | Incidence | Etiology | Symptoms | Diagnosis | Prognosis | Treatment |
|---|---|---|---|---|---|---|
| Hyperemesis gravidarum[3-17] | 1-20/1000 pregnancies (< 2%)[5] | Psychological predisposition<br>Hormones (human chorionic gonadotropin, estradiol)[7] | Severe nausea and vomiting<br>Dehydration<br>Malnutrition<br>Poor weight gain[1,7] | Diagnosis by clinical presentation (persistent vomiting, acute starvation and weight loss)<br>Increaed levels of liver enzymes (aminotransferase, alkaline phosphatase and amylase)[1,3,8-12]<br>Rarely, liver biopsy is needed[1,11,12] | Unchanged maternal and fetal outcomes after use of safe antiemetics<br>Increased risk of low-birth-weight infants, preterm birth, preeclampsia, and placental abruption in the 2nd trimester[8,16,17] | Avoid nausea triggering substances<br>Medical and supportive therapy (ginger, multivitamin or Vit B6 with H1 receptor antagonist doxylamine)<br>Treatment of dehydration (intravenous infusion of fluids, metoclopramide or promethazine with another H1 receptor antagonist dimenhydramine)[1,8,13-15] |
| Acute fatty liver of pregnancy[18-29] | 1/10000-15000 pregnancies[18] | Mutations in LCHAD[1,21] | Nausea, vomiting, anorexia lethargy, abdominal pain, ascites, progressive jaundice<br>Polyuria and polydipsia due to transient diabetes insipidus<br>Acute renal failure<br>Hepatic encephalopathy<br>Hypertension, proteinuria and edema[1,4,22,23] | Diagnosis by clinical and laboratory findings (increased levels of aminotransferases, ammonia, bilirubin, leukocytosis, hypoglycemia, thrombocytopenia, neutrophilia, coagulopathy, renal dysfunction)[20,22,24]<br>Tomography and ultrasonography are unremarkable[7]<br>Liver biopsy reveals microvesicular steatosis[25] | Liver function improves within a week to months[27]<br>Preterm delivery (75%) approximately at 34 wk gestation<br>Check all mothers with AFLP for defects in fatty acid oxidation[1] | Immediate hospitalization<br>Supportive measures (glucose infusion, readily availbale blood products)<br>Prompt delivery |
| Intrahepatic cholestasis of pregnancy[1,30-51] | 1-2/1000 pregnancies[1] | Multifactorial genetic (mutations in the *MDR3* gene)<br>Hormonal<br>Exogenous factors (*e.g.*, progesterone)<br>Abnormal biliary transport[25,33-35] | Generalized peripheral pruritus (1st sign)<br>Chills and abdominal pain<br>Diarrhea or steatorrhea[36,37] | Diagnosis by clinical symptoms and/or laboratory tests (increased levels of fasting serum bile acid and elevated bilirubin and transaminase levels)[38]<br>Liver biopsy is needed only in severe cases and biopsy reveals cholestasis with minimal or no inflammatory changes[39] | Good maternal outcome (laboratory results resolve within 2-8 wk postpartum)[7]<br>Compromised fetal outcome (spontaneous preterm labor, meconium-stained fluid with some perinatal mortality) in moderate and severe forms[1,42-46] | Symptomatic medical treatment (ursodeoxycholic acid: UDCA which is B Class safe drug for pregnancy and breastfeeding by FDA)[40,41]<br>Optimal timing of delivery at the best possible fetal maturity[45] |
| HELLP syndrome[1, 51-62] | 0.1%-0.6%[1,52] | Usually presents with preeclampsia (4%-12% are with severe preeclampsia)<br>Endothelial injury with fibrin deposit is the underlying mechanism of the disease[54] | Right upper quadrant or epigastric pain<br>Nausea and vomiting<br>Malaise<br>Nonspecific viral-like symptoms<br>headache<br>visual symptoms[55] | Liver biopsy is not necessary but if performed sinusoidal fibrin thrombin, hemorrhage, and hepatocellular necrosis might be observed[25]<br>Laboratory findings<br>Platelet count < 100000/μL<br>Serum aspartate aminotransferase > 70 U/L<br>Serum lactic dehydrogenase > 600 U/L[56] | Maternal death (1%)<br>Perinatal death (7.4%-20.4%)<br>Pulmonary edema<br>Acute renal failure<br>DIC<br>Abruptio placenta<br>Liver hemorrhage or failure<br>ARDS<br>Retinal detachment<br>Stroke<br>Blood transfusion related complications | Provide transfer to tertiary care center after confirmed diagnosis<br>Delivery > 34 weeks' gestation is recommended if possible<br>Prophylaxis of seizures with magnesium during labor and 24 h postpartum[58] |

HELLP: Hemolysis, elevated liver enzymes and low platelets; LCHAD: Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase; ARDS: Acute respiratory distress syndrome; AFLP: Acute fatty liver of pregnancy; FDA: Food and Drug Administration.

18.5% of cesarean deliveries were not elective or planned. When anesthesia and/or analgesia choices were evaluated in whole, we performed combined spinal epidural (CSE) for labor analgesia only in 1 patient. According to the records of cesarean deliveries, rates of neuraxial and general anesthesia were 85% and 15%, respectively. Among neuraxial anesthesia choices, spinal anesthesia (96%) was the mostly preferred one. Regarding neonatal outcomes, birth weight and Apgar scores were good as well. However,

there were 2 preterm births and 2 preterm labors from mild and severe IHCP cases (one from each). Hepatitis in 2 newborns was observed in parturients with mild IHCP. But the worst fetal outcome observed in a parturient having severe IHCP was perinatal fetal death at the 34 weeks' of gestation. Anesthesia choices for delivery might be challenging in IHCP. Due to the physiologic decrease in gall bladder contractility, pregnant women tend to have a sort of physiologic cholestasis. The cholestasis might lead to malabsorption of vitamin K. Vitamin K is a cofactor responsible from synthesis of coagulation factors Ⅱ, Ⅶ, Ⅸ and Ⅹ. Therefore, coagulation abnormalities might be expected in parturients with IHCP. Additionally, increased liver enzymes; aspartate aminotransferase (AST) and predominantly ALT are considered to be determinants of liver diseases[1,28,37,47-49]. However, in a recent retrospective study investigating the incidence of coagulopathy in parturients with IHCP, no abnormal coagulation studies were found even in the presence of significantly increased liver enzymes[50]. The authors reported that the presence of coagulopathy in parturients with isolated IHCP was low and the routine coagulation studies were not necessary except patients having IHCP with coexisting preeclampsia[50]. Similarly, we had neither abnormal coagulation parameters nor we came across any patient with coexisting preeclampsia in our study.

Severity of IHCP, especially bile acid levels higher than 40 μmol/L, may affect pregnancy outcomes[46,51]. Based on these studies, we similarly classified our cases having bile acid level ⩾ 10-39 μmol/L, 40-99 μmol/L and ⩾ 100 μmol/L as mild, moderate and severe IHCP, respectively. In the present study the rates of mild, moderate and severe IHCP were 65%, 21% and 14%, respectively. When we compared our studies in this regard, the incidence of mild IHCP was higher but severe IHCP was less than that of study by Brouwers *et al*[51]. In mild cases obstetric management includes delivery at 38 weeks' gestation but early delivery at 36 weeks' can be considered in severe cases due to the high risk of fetal distress/death, jaundice or unbearable maternal pruritis despite ursodeoxy cholic acid (UDC) treatment[28,37,47-51]. In contrast to the 14% of CS rate in Brouwers *et al*[51]'s study, we documented much higher CS rate, which was 73%. However, our high CS rate was consistent with 65% rate of DeLeon *et al*[50]. Currently, we have observed adverse outcomes including preterm labor and birth and perinatal fetal death in severe IHCP class parturients.

Pregnancy associated liver diseases and/or abnormalities in conjunction with their interpretation have been extensively studied[2,25,26,32]. Our maternal and fetal-neonatal outcomes according to the elevated bile acid levels were comparable to recent retrospective studies[50,51]. However, the present retrospective records including 37 cases with IHCP delivered in Gazi University in one-year period might be helpful to provide better understanding of anesthetic management. Consequently, parturients with IHCP having normal coagulation parameters despite increased liver enzymes preoperatively underwent cesarean delivery mostly under spinal anesthesia uneventfully. Although maternal outcomes were generally good, adverse fetal and neonatal outcomes may occur more likely in severe IHCP.

## HELLP SYNDROME

HELLP syndrome is commonly associated with hypertension, proteinuria, and edema develop either in the second or third trimester. HELLP syndrome has an incidence of 0.1%-0.6% that develops usually in the 3rd trimester. The rate of HELLP patients with severe preeclampsia is 4%-12%[52]. While 70% of patients with HELLP syndrome present before delivery, 30% of them develop in the postpartum period[1].

Some of the risk factors for HELLP syndrome are nulliparity and advanced maternal age[53]. The incidence, etiology, symptoms, diagnosis and treatment of HELLP syndrome were indicated in Table 1 as well[1,51-62].

Fifty percent of patients with HELLP syndrome might be free of all diagnostic criteria. Maternal morbidity varies due to the degree of thrombocytopenia. According to the Mississippi classification for HELLP, class 1 corresponds to platelet count ⩽ 50000/μL, class 2 corresponds to platelet count greater than > 50000 but ⩽ 100000/μL, while class 3 corresponds to platelet count 100000-⩽ 150000/μL[57].

HELLP syndrome often progresses and may eventually compromise maternal and fetal outcome. If diagnosis is controversial, hypertension should be controlled by available intravenous antihypertensive drugs (hydralazine or labetalol)[58].

Delivery is recommended ⩾ 34 weeks' gestation. Intravenous magnesium sulfate (4-g loading dose followed by 2 g/h) should be administered for seizure prophylaxis during labor and for 24 h postpartum[58]. In case of active labor, a vaginal delivery may be proceeded if there is no fetal distress or risk of disseminated intravascular coagulopathy. Additionally, in case of coexistence with multi-organ dysfunction, renal failure, or abruption, immediate cesarean delivery should be performed because induction of labor is not indicated.

Patients with HELLP syndrome generally receive platelet transfusion if the platelet count is < 20000/μL, if < 50000/μL and cesarean delivery is mandatory. There is no need to transfuse platelet more than once, since thrombocytopenia improves after delivery[59].

For choosing method of analgesia, epidural block is generally contraindicated if platelet count is less than 75000/μL but is also up to the experience of the anesthesiologist. Patients should be monitored for at least 48 h in the postpartum period to avoid pulmonary edema. Laboratory abnormalities usually regress 24 h postpartum and almost completely recover 48 h postpartum[1].

HELLP syndrome is associated with increased risk of maternal and fetal morbidity and mortality. Rate

of maternal death is approximately 1%. Noteworthy maternal complications include pulmonary edema, acute renal failure, DIC, abruptio placenta, liver hemorrhage or failure, ARDS, retinal detachment, stroke and adverse events due to blood transfusion[1].

The rate of perinatal death varies between 7.4%-20.4%, depending on the gestational age and concurrent factors related to the pregnancy. The highest morbidity and mortality rates are observed < 28 weeks' gestation[60]. Most perinatal morbidity is due to prematurity that may cause to RDS, bronchopulmonary dysplasia, intracerebral hemorrhage, and necrotizing enterocolitis.

General anesthesia for CS has been the most commonly preferred technique in HELLP syndrome. However, high rate of use of regional anesthesia for CS has been documented in a review of 102 cases with preterm HELLP syndrome[61]. According to review of 102 charts, number of antepartum and postpartum HELLP were 95 and 7, respectively. Mean gestational age was 30.6 ± 2.7 (23-36) wk. Most of the parturients underwent regional anesthesia ($n$ = 65). Cases having preoperative mean platelet count of 113000/μL ($n$ = 53) underwent CS under CSE, while spinal anesthesia was performed in pregnant women ($n$ = 12) having preoperative platelet count of 95000/μL. Interestingly, 2 patients with mean platelet count < 50000/μL underwent CS with CSE. One of these patients received platelet transfusion immediately before CSE. Luckily, epidural hematoma has not been reported in none of the patients received regional anesthesia[61].

However, subarachnoid hematoma following spinal anesthesia in a 39-year-old having G3, P2 (151 cm and 52 kg) with severe preeclampsia associated HELLP delivered at 27 weeks' gestation was reported. A 23 G Quincke spinal needle was used to inject 2.5 mL of hyperbaric bupivacaine for spinal block. Apgar scores of a 696 g of baby were 6 and 9 at 1 and 5 min, respectively. Duration of surgery was approximately 37 min with approximately 400 mL blood loss. Complete recovery of motor block was achieved 5 h after spinal anesthesia. Although preoperative platelet count was 91000/μL, it declined progressively to 30000/μL postoperatively (2$^{nd}$ day). Patient was suffering from numbness on the posterior aspect of her thigh and the toes of her right leg and her bladder was insensitive to fullness (urinary retention). Neurologic examination revealed flaccid paraparesis. Power in her right hip was 4/5, while it was 3/5 in her right knee, ankle and toes. There was sensory deficit in her right leg between L3-S5 dermatomes, while it was between L4-S5 dermatomes in her left leg. Spinal subarachnoid hematoma compressing cauda equina was observed in the magnetic resonance imaging. Medical treatment including Vit B12 and PG E1 against neurologic deficit, oral neostigmine + bladder exercise for urinary retention, flurbiprofen for relieving headache and neck pain and rehabilitation for paraparesis were performed. Complete recovery was observed 3 mo after conservative treatment (hematoma regression)[62].

## PRINCIPLES OF ANESTHETIC MANAGEMENT

Regional anesthesia is recommended in patients with advanced liver disease whenever possible because of the less systemic effects of the locally administered drugs. Regional anesthesia is superior than general anesthesia due to possible liver dysfunction leading to delayed metabolism of general anesthetic drugs. Either central or peripheral blocks could be considered in liver dysfunction and/or failure. Total drug dose used in peripheral block should be cautiously calculated and close monitoring is advocated for side effects[49]. Regarding local anesthetic drugs, $t_{1/2elim}$ of lidocaine increases 3 fold from 108 to 296 min. Meanwhile, increased volume of distribution (Vd) of lidocaine offers some protection against toxicity. α1 acid GP is synthesized even in end stage liver disease which provides some protection against toxicity as well. However, clearance of ropivacaine is less in the end stage liver disease than normal. For ester type local anesthetic drugs, though pseudocholin esterase enzyme production in the liver may decrease in disease state, overall clearance of chloroprocaine is unclear.

Although coagulopathy is an absolute contraindication for regional anesthesia, it can be recommended in selected patients having acceptable coagulation profile. Regional anesthesia blunts hemodynamic effects of stress hormones in the circulation. These hormones depress immune function as well[63]. In all cases, arterial blood pressure should be maintained and sympathetic stimulation should be avoided.

Considering general anesthesia, isoflurane seems to be a better choice[64]. When sevoflurane or desflurane were compared with isoflurane, sevoflurane could have some advantages over others without significant differences among them[65,66]. Nitrous oxide was used to be an inhalation anesthetic despite risk of accumulation of gas in the closed spaces leading to distension[49]. However, liver cell injury with xenon anesthesia has been shown to be impossible which might be a promising alternative agent[67].

Successful use of opioids has been reported in liver disease despite there were concerns with delayed drug clearance and prolonged half-life. Fentanyl, if used in relatively moderate doses, is a good choice without affecting oxygen supply, or requirements of the liver[68,69].

The rate of oddi sphincter spasm was nearly 3% due to opioids. Medical treatment can be provided with atropine, naloxane, glucagon, nitroglycerin, volatile anesthetics, or antispasmodic drugs. Anesthesia induction and maintenance are provided with possibly safe drugs and pulmonary and cardiovascular measures should be maintained. Anesthetic management using inhalation agents (isoflurane, desflurane or sevoflurane), alone or in combination with small doses of fentanyl

seems to be reasonable. Anesthetist must consider the altered pharmacokinetics in liver disease. Half-life of lidocaine and benzodiazepines may increase by more than 300% and 100%, respectively. Drugs, like sodium thiopentone, highly bound to albumin have a decreased Vd. Therefore, doses should be adjusted accordingly. Among intravenous anesthetic agents, propofol is the most favorable one for liver diseases. It has a short half-life even in cirrhosis. However, either edema or increased gamma globulin resulting in the increased Vd may require to increase the first effective dose of many drugs[49].

Long acting narcotics and sedatives should be avoided in cirrhotic patients. Fentanyl or sufentanil and oxazepam or lorazepam, in conjunction with sevoflurane or propofol are recommended[40,70].

For non-depolarizing muscle relaxants, vecuronium and atracurium are recommended because these muscle relaxants are not metabolized mainly in the liver. Clearance and elimination half-life of atracurium are preserved even in impaired liver or renal function. Because of larger Vd, elimination half-life is shorter in severe hepatorenal dysfunction than that of healthy individuals. Therefore, muscle relaxants are used guided by neuromuscular block monitoring[49].

Suxamethonium which is a depolarizing muscle relaxant is used for providing RSI. It has a prolonged half-life due to decreased serum cholinesterase concentrations in liver dysfunction and during pregnancy.

Both vecuronium and rocuronium have prolonged elimination in severe cases. Either atracurium or cisatarcurium may be a better option because of independent metabolism of liver and kidney[71].

Consequently, rational selection of anesthetic drugs and close monitoring are the key factors for providing safe anesthesia.

## POSTOPERATIVE CARE

Even though delayed clearance is a concern in severe liver disease, intravenous opioids can be administered for postoperative analgesia. Neuraxial opioids, especially a single dose of morphine, may obviate any accumulation issues. Advanced liver disease can lead to hepatic encephalopathy. Neurologic deterioration in the postoperative period may result from the residual effects of anesthetic agents, acute liver decompensation, or an intracranial process. Neurologic observation and liver function monitoring is essential to the proper postoperative management of pregnant women with advanced liver disease[49].

## SPECIFIC ANESTHETIC CONSIDERATIONS

Pregnant woman with either mild IHCP or uncomplicated liver transplantation may be managed in the same manner as a healthy parturient assuming that hepatic synthetic and metabolic functions were intact. Only coagulopathy should be excluded or corrected before regional anesthesia if possible[1].

According to a retrospective cohort study including 319 parturients with or without coagulation tests, no neuraxial hematoma was observed even in case of liver enzyme elevations > 5 times than normal. Postpartum hemorrhage after vaginal or cesarean delivery was 2.4% and 6.3%, respectively. Based on these results, routine coagulation test monitoring in IHCP to minimize neuraxial anesthesia complications or predict postpartum hemorrhage was not necessary. Therefore, neuraxial anesthesia is not necessarily be delayed or avoided in pregnant patient with IHCP[50].

Anesthesia selection for AFLP should be individualized. General anesthesia with RSI is recommended in case of severe coagulopathy. Perioperative anesthetic care includes establishing adequate iv access with readily available cross matched blood and blood products since PPH is anticipated[49].

In summary, particularly spinal anesthesia is the 1st choice for patients with HELLP syndrome scheduled to undergo CS if there is no progressive thrombocytopenia. Close patient monitoring is a must against hemorrhagic complications, DIC or ecclampsia at all times. If neuraxial anesthesia is contraindicated, general anesthesia with RSI should be performed especially in hypertensive patients. Additionally, risk of aspiration due to full stomach and/or difficult airway should be taken into account. General anesthesia is indicated as a 1st option when platelets < 80000/μL (class 1 or partially class 2 HELLP syndrome)[71].

In conclusion, selection of either general or regional, or MAC alone may not be sufficient enough for good survival and better outcomes because induction of a safe anesthesia in this specific group needs special attention and care with rational choice of drugs under constant careful monitoring. Prevention of further liver injury can be provided by optimizing hepatic blood flow and oxygenation. Effects of anesthesia type and local and general anesthetic drugs on the liver should be carefully considered as well.

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MINIREVIEWS

# Awareness during anesthesia: Current status in Japan

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## Abstract

Intraoperative awareness is the explicit recall of sensory perceptions during general anesthesia. I presume the epidemiology and characteristics of intraoperative awareness from these surveys in Japan. A questionnaire survey was conducted *via* the Internet. The first survey was conducted in 2008. Our survey showed 17% of anesthesiologists experienced definite or possible awareness. The second survey was conducted to evaluate the first survey in detail in 2008. A total of 172 anesthesiologists answered. The total number of reported anesthetic cases was 85156. Twenty-four cases of definite or possible awareness were reported by 21 anesthesiologists. The most surprising finding was total intravenous anesthesia (TIVA) was used in 21 of the 24 cases. The third survey was conducted in 2011 as a continuous survey. Six cases of definite or possible awareness were reported by six anesthesiologists (7%). Two cases were maintained by TIVA, and 2 cases were sevoflurane. The survey showed 76% anesthesiologists routinely use bispectral index (BIS) for TIVA, but for sevoflurane only 27% anesthesiologists routinely use BIS. The incidence of intraoperative awareness decreased in the third survey. The continuous survey revealed the current status of daily anesthesia and the results might be used to prevent the awareness during general anesthesia.

**Key words:** Awareness; Bispectral index; Sevoflurane; Total intravenous anesthesia



**Core tip:** The epidemiology and characteristics of intraoperative awareness from these surveys in Japan are reviewed in this manuscript. The incidence of intraoperative awareness decreased in the third survey. The continuous survey revealed the current status of daily anesthesia and the results might be used to prevent the awareness during general anesthesia.

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## INTRODUCTION

Intraoperative awareness is a rare but still serious

problem in clinical anesthesia. It is defined as ann explicit recall of sensory and auditory awareness during general anesthesia. The incidence of intraoperative awareness has been reported as 0.1%-0.2%[1,2]. Although this problem is rare, some patients might suffer prolonged psychological side effects, including post-traumatic stress disorders.

Widespread changes have occurred after the introduction of remifentanil in Japan in 2007. This caused a reduction of the maintenance dose or concentrations in volatile anesthesia. These changes might induce the increase in the incidence of intraoperative awareness. Therefore, we conducted three separate questionnaire surveys of anesthesiologists from 2008 through 2011. From the results of these surveys, we were able to make presumptions about the epidemiology and characteristics of intraoperative awareness, and discuss recommendations to decrease its incidence.

## THE FIRST SURVEY

Remifentanil was released in Japan in 2007, followed by widespread changes in anesthesiology procedures. The doses of anesthetics used in combination with remifentanil might decrease. Moreover, the choice of total intravenous anesthesia (TIVA) increased. These changes might have increased the incidence of awareness.

The incidence of awareness during general anesthesia has not been evaluated prospectively in Japan. Therefore, we conducted a questionnaire survey in 2008[3]. The purpose of the survey was to assess the status of anesthesia after the release of remifentanil and the incidence of intraoperative awareness during remifentanil anesthesia.

Letters were sent to the chief staff anesthesiologists in Japanese hospitals to response the survey. The responders answered the survey questions anonymously on an open access website. It was designed to acquire the information concerning daily clinical anesthesia, choice of anesthetics, and experiences of intraoperative awareness during 2007.

### *Awareness cases in the first survey*

A total of 145 anesthesiologists responded to the survey. Five (3%) anesthesiologists reported cases of definite awareness, and 21 (14%) anesthesiologists reported cases of possible awareness.

The relationship between daily anesthesia practice and experience with intraoperative awareness was evaluated. Concerning the standard maintenance concentration of sevoflurane in combination with remifentanil, 7% of the anesthesiologists used 0.7%, 44% used 1%, 30% used 1.2%, and 16% used 1.5%. These low concentrations might be explained by the manufacturer's usage guide for remifentanil stating that sevoflurane should be used at a 1.0% concentration in combination with remifentanil. The choice of sevoflurane concentrations might also have been influenced by a report by Manyam *et al*[4] that recommended 0.75% sevoflurane in combination with remifentanil. Figure 1 shows the relationship between cases of awareness reported by the anesthesiologists and their standard maintenance sevoflurane concentration. The anesthesiologists who experienced definite awareness cases maintained sevoflurane concentrations below 1.0%. Cases of intraoperative awareness were significantly lower for anesthesiologists who maintained sevoflurane concentrations above 1.2% than for those who maintained concentrations below 1.0%. This result is compatible with a study by Avidan *et al*[5] that found the incidence of awareness in patients maintained with end-tidal volatile anaesthetic concentrations above 0.7 minimum alveolar concentration (1.2%-1.4% sevoflurane) was 0.1%, which is compatible with the incidence in patients maintained at target bispectral index (BIS) values between 40 and 60. Our results show that, after the release of remifentanil, the incidence of intraoperative awareness might have been higher because 17% of anesthesiologists experienced definite or possible awareness cases in one year. Maintaining sevoflurane concentrations below 1.0% might be associated with a high risk for intraoperative awareness. Our results indicate that maintaining volatile anesthetic concentrations is the most important factor in preventing intraoperative awareness.

## THE SECOND SURVEY

To get more detailed information, the second survey was planned[6]. The second survey was planned to obtain information concerning the cases involving intraoperative awareness in 2008. The survey method was similar to that of the first survey. A total of 172 anesthesiologists responded to the second survey. The total number of general anesthesia cases in 2008 was 85156 in this survey. Twenty-one anesthesiologists reported 24 cases of definite or possible awareness, of which 14 were cases of definite awareness and 10 were possible awareness. One patient experienced definite awareness twice, and another patient suffered possible awareness three times. The incidence of intraoperative awareness, including cases of possible awareness, was 0.028%. Many previous studies demonstrate a higher incidence of about 0.2%[1,2]. However, the results of a retrospective study revealed that the actual incidence of awareness is underestimated. For example, a recent report[7] from the Fifth National Audit Project (NAP5), the national United Kingdom survey of intraoperative awareness during general anesthesia based on voluntary reporting by doctors, estimated that the incidence of awareness in general anesthesia was as low as 1:15414. Our survey results are consistent with the results of a retrospective study reported by Mashour *et al*[8]. The results of our study indicate that the incidence of awareness during anesthesia in Japan is compatible

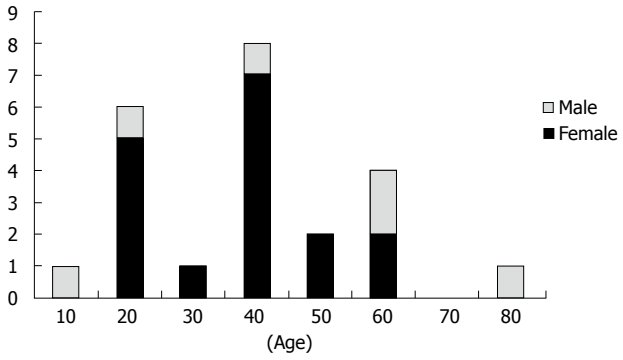


**Figure 1 Patient demographics of definite and possible awareness cases.** Sixteen (67%) were < 50 years old, 6 (26%) were men, and 17 (74%) were women.

with the incidence reported in other countries.

### *Awareness cases in the second survey*

The most surprising finding from the second survey was that propofol was used as the anesthetic in TIVA in 21 of the 24 cases. Therefore, our results provide information about the characteristics of awareness in TIVA. Based on the data about daily anesthesia acquired from the survey, 16% of anesthesiologists reported using mostly propofol, 17% used more propofol than volatile anesthetics, 9% used propofol and volatile anesthetics equally, 26% used more volatile anesthetics than propofol, and 32% used mainly volatile anesthetics. This result indicates that volatile anesthetics were chosen more commonly than propofol. Our survey indicates that TIVA might be a risk for intraoperative awareness.

TIVA's role as a risk for intraoperative awareness is still controversial. No prospective studies evaluated the incidence of awareness between the anesthetics. However, some studies have stated to TIVA as a risk factor for awareness[9]. One reported risk is associated with the failures of infusion pumps. The absence of real-time feedback of blood anesthetic concentrations might also be a risk factor. Moreover, the inter-individual variability in need of anesthetics essential to prevent movement during the noxious stimulation may be not as much of volatile anesthetics than TIVA[10]. The target-controlled infusion system predicts the plasma anesthetics concentrations, which might be different from the actual concentration. Therefore, the use of brain monitoring, including BIS, is essential. In our survey, BIS monitoring was used in seven (33%) out of 21 awareness cases that were maintained by TIVA. This shows that the use of a BIS monitor could not prevent all cases of awareness. The usefulness of BIS to prevent awareness in TIVA should be evaluated in a future study.

In our survey, 16 (67%) of the patients experiencing awareness during general anesthesia were below 50 years of age, and the majority of patients were female (Figure 1). Similarly, previous studies showed that the incidence of awareness is higher in female patients[11]. Moreover, women recovered from propofol anesthesia more rapidly than men[12]. This might indicate that women are less sensitive to propofol.

**Table 1 Descriptions of awareness cases**

| Case | Age | Sex | Anesthetics | BIS monitoring | Detail |
|---|---|---|---|---|---|
| 1 | 30 | M | Sevoflurane | - | Low sevoflurane concentration before surgery |
| 2 | 50 | M | Sevoflurane | + | Low sevoflurane concentration during bleeding |
| 3 | 70 | F | TIVA | - | |
| 4 | 80 | F | TIVA | - | Trouble in infusion pump |

BIS: Bispectral index; TIVA: Total intravenous anesthesia; M: Male; F: Female.

The reported surgical procedures included one craniotomy, four facial operations, seven neck and chest wall operations, one cardiac operation, three gynecologic operations, three operations for fractures of the leg, and one spinal operation. The results indicate that the surgical procedures with the highest risk for awareness are cervicofacial and chest wall surgery. In brief, surgery in the upper part of body produced the highest risk of awareness. Gynecologic and orthopedic procedures were the next most likely to be associated with intraoperative awareness.

The high incidence of awareness in cervicofacial surgery[2] has not reported previously. Although the reasons are unclear, it is thought that visual and auditory stimulation during surgery play a part[12]. The higher risk during orthopedic surgery supports this hypothesis because elevated levels of acoustic stimulation are common during orthopedic operations. There might also be an increased risk of awareness when general anesthesia is maintained by TIVA.

## THE THIRD SURVEY

The third survey was conducted in 2011 as a continuous survey[13]. We particularly sought to evaluate whether TIVA is a risk factor for intraoperative awareness. The survey was designed to obtain information regarding cases involving intraoperative awareness in 2010. Responses were received from 119 anesthesiologists. Because of incomplete data, only 91 responses were analyzed. Respondents reported 29340 general anesthesia cases in 2010; volatile anesthetics were used in 18109 cases, and propofol was used in 10184 cases.

Anesthesiologists reported six cases of definite or possible awareness. By the third survey, the incidence of awareness, including possible awareness, was 0.02%. This result is similar to the result of the second survey. Sevoflurane and propofol were used for maintenance of general anesthesia in four cases, two cases for each anesthetic (Table 1). The remaining two cases involved caesarean deliveries. Therefore, the incidence of intraoperative awareness in procedures

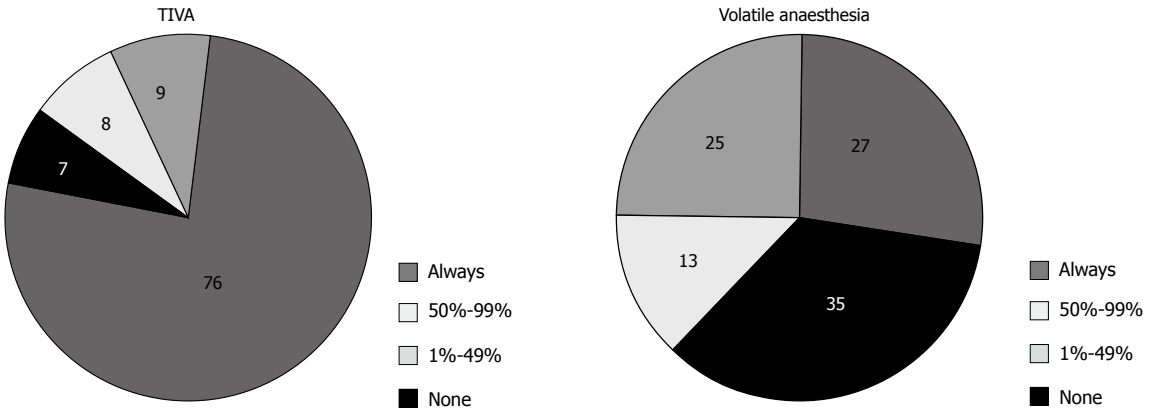


**Figure 2 Use of bispectral index monitoring in total intravenous anesthesia or volatile anesthesia.** Use of BIS monitoring was more frequent during TIVA than volatile anesthesia. BIS: Bispectral index; TIVA: Total intravenous anesthesia.

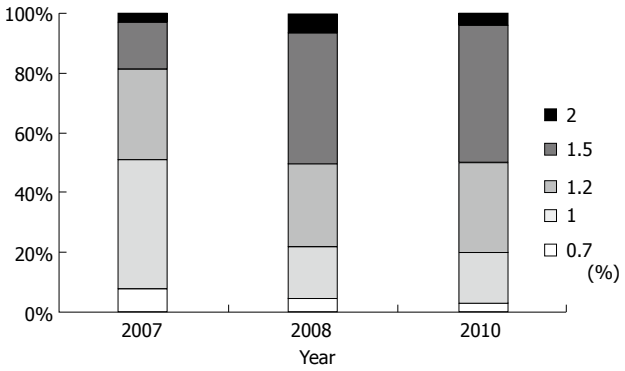


**Figure 3 Standard maintenance sevoflurane concentration for daily clinical anesthesia in the three surveys.**

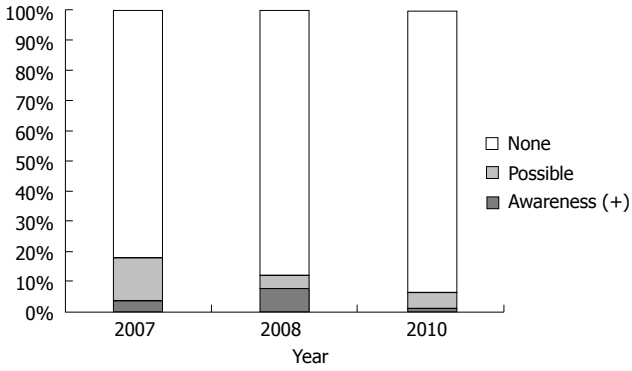


**Figure 4 The experience of awareness cases by respondents in the three surveys.** Experience of awareness decreased in the third survey.

with volatile agents and TIVA was 0.011%, and 0.019%, respectively. The difference in the incidence of awareness between volatile anesthesia and TIVA was not statistically significant ($P = 0.622$).

The survey results show that 74% of anesthesiologists routinely used BIS for TIVA, but only 28% of anesthesiologists routinely used BIS for volatile anesthesia (Figure 2). Use of BIS monitoring was more frequent during TIVA than volatile anesthesia ($P < 0.01$). These results suggest that anesthesiologists feel that there is a need for BIS monitoring when they use TIVA for maintenance of general anesthesia, perhaps because propofol has a wide variability in dosing.

The results of our second survey, which showed that TIVA was a risk factor for awareness, might have affected the frequency with which anesthesiologists used BIS monitoring. This concept is supported by the results of a review by Avidan *et al*[5]. The authors recommended using an end-tidal anesthetic concentration alarm rather than BIS when a volatile agent is used as the primary anesthetics. On the other hand, they suggested using BIS when volatile anesthetics are not used, because BIS monitoring prevents awareness in TIVA.

In one of two reported awareness cases, the patient might have awakened when sevoflurane was maintained at a low concentration before surgery; in the second case, the patient might have awakened when the sevoflurane concentration dropped because of hypotension caused by massive blood loss. These awareness cases could have been prevented if the sevoflurane concentration had been maintained above a certain level. There should be a further decrease in the incidence of awareness shortly.

## COMPARISON OF RESULTS OF THE THREE SURVEYS

We conducted three surveys at separate times. The results were quickly disseminated to Japanese anesthesiologists after each survey. Figure 3 shows the standard maintenance sevoflurane concentration for daily clinical anesthesia reported in each of the three surveys. In the first survey, only 20% of the anesthesiologists used a sevoflurane concentration above 1.5%. However, in the second and third surveys, about 50% of the anesthesiologists used sevoflurane concentrations above 1.5%. This increased use of higher sevoflurane concentrations might be the reason for the lower incidence of awareness under sevoflurane reported in the second and third surveys. In the first survey, 18% of the anesthesiologists experienced cases

of intraoperative awareness, including possible cases. However, this decreased to 7% in the third survey (Figure 4). Moreover, the tendency of TIVA to be a risk factor for intraoperative awareness was not observed. The continuous survey revealed the current status of anesthesia in Japan, and the results might be used to prevent awareness during general anesthesia.

In conclusion, awareness with explicit recall during general anesthesia remains a problem that should be prevented. Understanding the incidence of awareness and the status of daily anesthesia are one possible approach to a cure for this problem.

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ORIGINAL ARTICLE

Retrospective Study

# Intrathecal morphine *vs* femoral nerve block for postoperative-analgesia after total knee arthroplasty: A two-year retrospective analysis

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## Abstract

### *AIM*

To compare the efficacy of intrathecal morphine and single shot femoral nerve block for patients undergoing primary total knee arthroplasty.

### *METHODS*

Data was extracted from electronic medical records and case-paper record files of patients who underwent unilateral primary total knee arthroplasty under spinal anesthesia using bupivacaine 12.5 mg with intrathecal morphine (ITM) 0.2 mg and under general anesthesia (GA) with single shot femoral nerve block (FNB) using 20 mL 0.5% bupivacaine at our hospital in 2013 and 2014. All patients had received peri-articular infiltration as per the hospital protocol. Data for gender, age, weight, American Society of Anesthesiologists status, total surgical time, postoperative pain score using visual analogue scale (VAS) from 1 to 10 at 6 h, 12 h and 24 h postoperatively, 24 h opioid consumption, use of oral multimodal analgesia, postoperative high dependency unit (HDU) admission and the time to discharge from the hospital was collected. The data was analyzed using Mann-Whitney *U* test for continuous variables and Fischer's exact-*t*-test for categorical variables.

### *RESULTS*

Twenty-two patients in ITM group and 32 patients in FNB group were analyzed. Median pain scores using VAS in ITM group were significantly lower at 6 h (0.0 *vs* 2.0, $P < 0.001$), 12 h (0.0 *vs* 2.0, $P < 0.001$) and 24 h (0.0 *vs* 2.0, $P < 0.001$) postoperatively. Also,

postoperative morphine consumption in ITM group was significantly lower ($P < 0.001$). However, median of non-steroid anti-inflammatory drug unit requirement in 24 h postoperatively was statistically significant higher in ITM compared to FNB group (2.0 *vs* 1.0, $P = 0.025$). The difference in postoperative paracetamol consumption in 24 h was not statistically significant ($P = 0.147$). There was no significant difference in the postoperative HDU admission or time to discharge from the hospital. No respiratory depression in either group was noticed.

***CONCLUSION***

The ITM group patients had much lower pain scores and morphine requirement in the first 24 hour post-operatively compared to FNB group.

**Key words:** Postoperative analgesia; Intrathecal morphine; Femoral nerve block; Total knee arthroplasty; Pain after total knee arthroplasty



**Core tip:** In this retrospective analysis, intrathecal morphine (ITM) with spinal anesthesia and single shot femoral nerve block (FNB) with general anesthesia were compared in 54 patients undergoing primary total knee arthroplasty over two years at our institute. Pain scores and morphine consumption in 1st 24 h after surgery were significantly lower in ITM group compared to FNB group ($P < 0.001$); while complication rates, high dependency unit admission rates, and time to discharge from the hospital were similar in both groups. Also, patients in ITM group were highly satisfied ($P < 0.001$).

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## INTRODUCTION

Total knee arthroplasty (TKA) leads to considerable post-operative pain, which requires optimal control for early mobilization as per the current trend. Femoral nerve block (FNB) and intrathecal morphine (ITM) are commonly used techniques for postoperative analgesia since the recommendation by PROSPECT group[1] as a part of multimodal technique with non-steroid anti-inflammatory drugs and centrally acting drugs like paracetamol and systemic opioids. To compare the efficacy of these methods, we performed a retrospective analysis of patients who underwent unilateral primary TKA with single shot FNB with general anesthesia (GA) and ITM with spinal anesthesia (SA) in the year 2013 and 2014 at our hospital. Earlier, low dose ITM and ultrasound guided FNB have been compared albeit both groups had received SA[2]. In this study, Frassanito *et al*[2] 0.1 mg ITM was found to be safe and more efficient compared to single shot FNB using 25 mL 0.75% ropivacaine though the lower pain scores and morphine consumption in ITM group compared to FNB group were not statistically significant.

## MATERIALS AND METHODS

### *Methods*

After permission from the hospital ethics committee, and approval by SingHealth centralized institutional review board, data was extracted from electronic medical records for all patients who underwent unilateral primary TKA in the year 2013 and 2014. Only those patients who underwent primary TKA under SA using bupivacaine 12.5 mg with ITM 0.2 mg and those who underwent primary TKA under GA with FNB using 20 mL 0.5% bupivacaine at our hospital in 2013 and 2014 were included in this analysis. The case-paper record files were also obtained at this stage and looked into.

In the ITM group, 0.2 mg morphine was mixed with bupivacaine while performing SA. Preservative free morphine is supplied in ampoules of 10 mg in 1 mL. The person performing SA diluted preservative free 10 mg morphine with 9 mL of normal saline to obtain 1 mg/mL under aseptic precautions. From this diluted morphine, 0.2 mL was taken using insulin syringe and mixed with 2.5 mL of isobaric 0.5% bupivacaine. Lumber puncture was performed under asepsis using either Quincke or Whitacare spinal needle of 25 G and the mixture of bupivacaine and morphine was injected slowly. Only patients who received this dose of morphine and bupivacaine were included in this analysis for uniformity. In the FNB group, FNB was performed before the induction of GA and its effectiveness was confirmed by checking loss of sensation on the medial aspect of leg just below the knee before the start of GA. All FNBs were performed using ultrasound guidance and 22 G Stimuplex needle A50 (by B. Braun Medical Inc. - a stimulating non-echogenic single shot 50 mm needle). GA was induced with appropriate dose of propofol, fentanyl and atracurium and airway maintenance was with laryngeal mask airway. GA was maintained with oxygen, sevoflurane and intermittent doses of morphine. Only patients who received 20 mL of 0.5% bupivacaine for FNB were included in this study for uniformity. Patients who received a different dose of bupivacaine or ropivacine were not included. Patients who received continuous FNB, FNB plus sciatic block, SA with FNB or any other combination were not included in this analysis.

All patients in both groups had received intra-operative peri-articular infiltration as per the hospital protocol; a mixture of 20 mL of 0.5% bupivacaine with 30 mg ketorolac, and 5 mg morphine plus 20 mL normal saline. In FNB group, the surgeon carried this out at least 120 min after FNB was performed to avoid

**Table 1 Demographic data**

| | ITM ($n$ = 22) | FNB ($n$ = 32) | Statistical significance |
|---|---|---|---|
| Median (IQR) age: Years | 69.0 (62.8-74.3) | 61.0 (57.0-67) | $P$ = 0.002 |
| Sex: Numbers | | | |
| Male | 9 (37.5%) | 15 (62.5%) | $P$ = 0.665 |
| Female | 13 (43.3%) | 17 (56.7%) | |
| Median (IQR) weight: Kg | 64.3 (53.2-77.2) | 67.3 (61.2-80.2) | $P$ = 0.275 |
| Median (IQR) ASA status | 3.0 (2.0-3.0) | 2.0 (2.0-3.0) | $P$ = 0.161 |
| Median (IQR) total surgery time in minutes | 117.5 (108.8-135.0) | 107.5 (86.3-128.8) | $P$ = 0.163 |

IQR: Interquantile range; *n*: Numbers; ITM: Intrathecal morphine; FNB: Femoral nerve block.

local anesthetic toxicity.

Data for gender, age, weight, total surgical time, ASA status, postoperative pain scores using visual analogue scale (VAS) from 1 to 10 on flexion of the operated knee at 6, 12 and 24 h postoperatively, 24 h opioid consumption, use of oral multimodal analgesia, postoperative high dependency unit (HDU) admission and the time to discharge from the hospital was collected.

All patients had received $O_2$ 2 lit/min through nasal prongs for the first 12-h after the surgery. Also, we looked for complications such as postoperative nausea and vomiting (PONV), respiratory depression, urinary retention and itching. We defined respiratory depression for this study as respiratory rate < 8/min or $SaO_2$% < 94%.

Postoperatively, all FNB group patients were prescribed patient controlled analgesia (PCA) with morphine while ITM patients were prescribed intravenous tramadol on as required (PRN) basis. For calculations, tramadol 100 mg was considered equivalent to 10 mg morphine[3]. Diclofenac, eterocoxib and celecoxib were used orally on PRN basis in both groups. One unit of non-steroidal anti-inflammatory drugs (NSAIDs) was considered as 50 mg diclofenac or 90 mg eterocoxib or 200 mg celecoxib. Patients in both groups were given paracetamol 1 g on PRN basis.

A backward sample size calculation was done for this retrospective study: With a standard deviation (SD) of 10 mg and clinical relevant difference of 10 mg between ITM and FNB (in a ratio of 1:1.5) for the amount of post-operative morphine consumption, the minimum sample size of 20 patients for ITM and 30 patients for FNB were required for a significance level of 5% and power of 90%.

The data was analyzed using Mann-Whitney *U* test for continuous variables and Fisher's Exact test for categorical variables. Patient satisfaction was evaluated from the discharge feedback form.

Ms Carmen Kam Jia Wen, research officer at "Clinical and Trial and Research Unit" (CTRU) at Changi General Hospital, Singapore helped and reviewed this statistical analysis.

## RESULTS

There was no statistically significant difference between two groups as far as the gender, weight, ASA status and total surgery time was concerned ($P$ > 0.05). However, median age was significantly older in ITM group than FNB group (69 years *vs* 61 years, $P$ = 0.002) (Table 1). Patients who received additional blocks or continuous femoral block or combined technique were excluded from the analysis. Twenty two patients in ITM group and 32 patients in FNB group were analyzed.

Median pain scores in ITM group were significantly lower at 6 h (0.0 *vs* 2.0, $P$ < 0.001), 12 h (0.0 *vs* 2.0, $P$ < 0.001) and 24 h (0.0 *vs* 2.0, $P$ < 0.001) post-operatively. Also, median of postoperative morphine consumption in ITM group was significantly lower ($P$ < 0.001). However, median of NSAID (unit) requirement in 24 h postoperatively was statistically significant higher in ITM compared to FNB group (2.0 *vs* 1.0, $P$ = 0.025). The difference in postoperative paracetamol consumption in 24 h was not statistically significant ($P$ = 0.147).

There was no statistically significant difference in the postoperative HDU admission or time to discharge from the hospital.

All patients in ITM group were prescribed antiemetic at regular time interval and hence did not have any incidence of PONV. While the patients in FNB group were prescribed antiemetic on PRN basis; for this reason the incidence of PONV cannot be compared. There were a number of patients who reported PONV in FNB group: 16 patients at 6 h, 11 patients at 12 h and 9 patients at 24 h. Use of sevoflurane and morphine can also cause PONV. Also, a urinary catheter was electively placed for 24 h for all patients in ITM group and hence urinary retention could not be assessed. The results are presented in the Table 2 and Figures 1-3.

## DISCUSSION

In this two-year retrospective analysis, patients who received 0.2 mg ITM had much lower pain scores and lower morphine requirement in the first 24 hour postoperatively compared to patients who received FNB using 20 mL of 0.5% bupivacaine.

The pain scores using VAS are recorded by our acute pain service nurses every 6 h for the first 24 hour postoperatively when ITM is given or single shot peripheral or neuraxial blocks are given. Only when the catheters are placed for peripheral or neuraxial blocks or PCA pumps are attached, the acute pain service nurses would evaluate these patients for pain beyond 24 h till the catheters or PCA pumps are removed. For this reason we could not analyze the data for pain beyond 24 h postoperatively.

TKA causes a lot of pain postoperatively. Current trend amongst most surgeons is to mobilize the

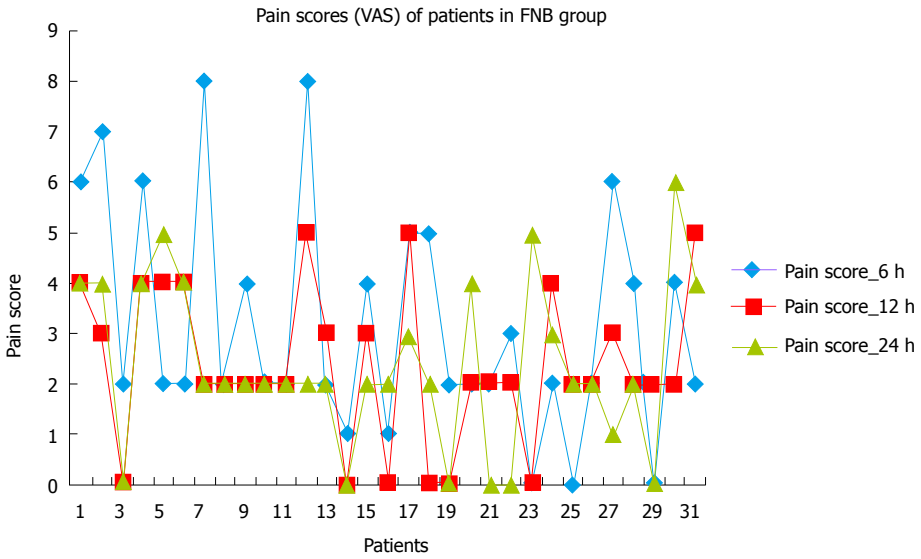


**Figure 1 Pain scores at 6, 12 and 24 h in femoral nerve block group.** ITM: Intrathecal morphine; FNB: Femoral nerve block; VAS: Visual analogue scale.

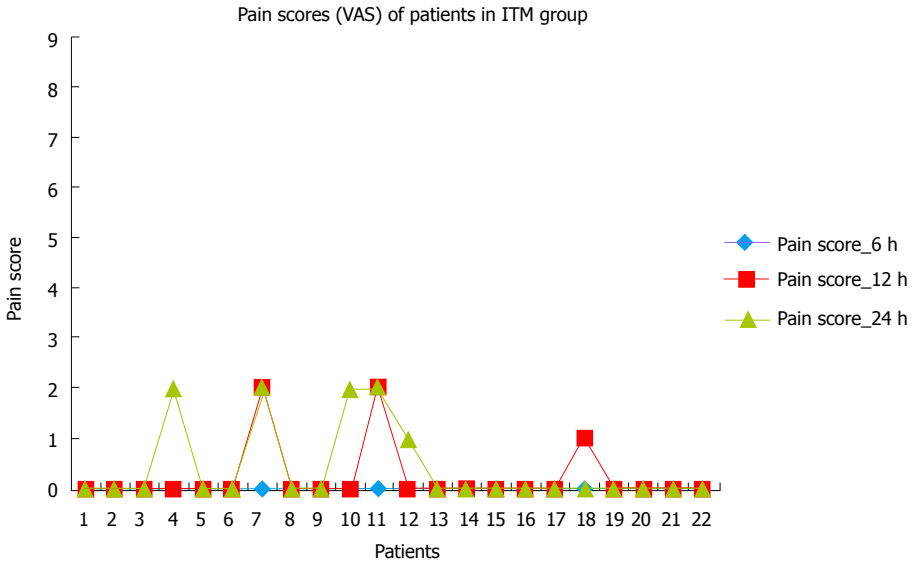


**Figure 2 Pain scores at 6, 12 and 24 h in intrathecal morphine group.** ITM: Intrathecal morphine; FNB: Femoral nerve block; VAS: Visual analogue scale.

patients early and discharge from the hospital as early as possible. Hence good pain control in immediate postoperative period is imperative for early mobilization and full flexion recovery.

ITM provides excellent post-operative analgesia and with low dosage it gives segmental analgesia, resulting in localized nociception without motor, sensory or autonomic side effects[4]. Late last century very large dose up to 4 mg ITM was used while today the dose ranges from 0.1-0.5 mg, depending on the type of surgery[5]. In one meta-analysis, it was shown that the use of ITM at dose < 0.3 mg, the rate of episodes of respiratory depression was not higher compared to the placebo group who received systemic opioids[6]. In our analysis where 0.2 mg ITM was used, no respiratory depression was recorded. Other undesirable side effects of ITM are itching, urinary retention and PONV. All patients who had received ITM in our analyses had indwelling urinary catheter for the first 24 h. Also they received round the clock prophylactic antiemetic and hence no patient suffered from PONV.

Regional and peripheral nerve blocks are promising inclusions in multimodal analgesia techniques. According to one study, femoral nerve block is still the gold standard for an effective analgesia approach in knee arthroplasty and should be supplemented (if needed) by oral opioids[7]. Femoral nerve block is frequently used as a part of multimodal technique for postoperative analgesia after TKA all over the world. In a meta-analysis by Paul *et al*[8], single shot FNB or continuous FNB plus patient controlled analgesia (PCA) was found to be superior to PCA alone for postoperative analgesia for patients having TKA. The impact of adding a continuous FNB to a single shot FNB was not found to be superior and further investigations were suggested by the authors. The use of single shot FNB was frequent

**Table 2 Results**

| | ITM ($n$ = 22) | FNB ($n$ = 32) |
|---|---|---|
| Ease of performance | Very easy, no special training | Expertise and training required, special equipment required |
| Added cost | Only morphine | Ultrasound machine, special needle and local anesthetic |
| Median (IQR) pain score at: | Low | High |
| 6 h | 0.0 (0.0-0.0) | 2.0 (2.0-4.8) |
| 12 h | 0.0 (0.0-0.0) | 2.0 (2.0-3.8) |
| 24 h | 0.0 (0.0-0.3) | 2.0 (2.0-4.0) |
| Median (IQR) of morphine requirement (in mg) in 24 h | Low 5.0 (3.8-10.0) | High 16.5 (8.0-21.5) |
| Median (IQR) of NSAID unit in 24 h | 2.0 (1.0-2.0) | 1.0 (0.0-1.3) |
| Median (IQR) of Paracetamol (G) in 24 h | 3.0 (2.0-3.0) | 3.0 (2.0-4.0) |
| Complications | Low | Low |
| | No PONV since antiemetic prescribed in anticipation | Incidence of PONV was higher since no regular antiemetic given (16 at 6 h, 11 at 12 h and 9 at 24 h) |
| | No urinary retention since all patients were catheterized | No urine retention |
| | No respiratory depression | No respiratory depression |
| | No itching recorded | No itching recorded |
| Number of elective HDU admission status | 3 (15%) | 2 (6.5%) |
| Median (IQR) days to discharge | 4.5 (3.0-5.0) | 4.0 (3.0-6.0) |
| Patient satisfaction | 18/20 (90.0%) rated good | 4/31 (12.9%) rated good |

IQR: Interquantile range; $n$: Numbers; ITM: Intrathecal morphine; FNB: Femoral nerve block; PONV: Post-operative nausea and vomiting; HDU: High dependency unit.

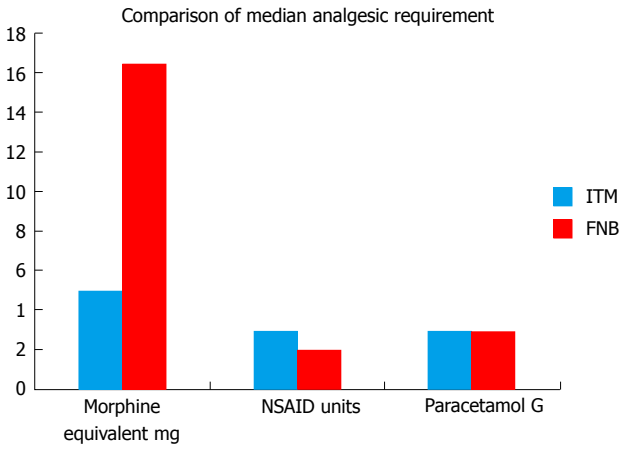


**Figure 3 Comparison of median analgesic requirement in 24 h.** ITM: Intrathecal morphine; FNB: Femoral nerve block: NSAID: Non-steroid anti-inflammatory drug.

at our hospital in 2013 and 2014. Also, single shot FNB can have analgesic effect from 12 to 24 h[9,10] and may extend up to 48 h[11]. Similarly analgesic effect of ITM also lasts for around 24 h and hence it is only fair to compare ITM and single shot FNB for their efficacy for postoperative analgesia.

In a meta-analysis by PROSPECT working group[1], for joint replacement surgery GA combined with an FNB for surgery and postoperative analgesia, or SA with local anesthetic plus ITM is recommended. The group also recommends cooling and compression techniques, paracetamol and conventional NSAIDs or COX-2-selective inhibitors, plus intravenous strong opioids (high-intensity pain) or weak opioids (moderate- to low-intensity pain) for postoperative analgesia. At our institute we follow these recommendations. In addition, the surgical team also prefers to use local infiltration technique as described earlier.

FNB requires the use of ultrasound machine and a special needle, which add to the cost. Also, an expertise in performing the FNB is necessary for good outcome. Additional time to perform and to evaluate the block is also required. In addition, there is a possibility of motor weakness which can increase the risk of postoperative fall. ITM is very cost effective, time saving and a relatively simple technique. Having these considerations on our mind we decided to analyze the outcome for these two techniques and found that ITM group had lower pain scores in the first 24 hour after surgery though the number of patients that we could include was small.

We found three more clinical trials in the literature comparing ITM and FNB for primary unilateral TKA but in all three trials both groups had received SA. In the study published by Frassanito *et al*[2], where SA was used for both ITM and FNB group, the 24 h and 48 h morphine consumption was lower in ITM group though not statistically significant. In this prospective study, a very low dose of ITM of 0.1 mg was used. In another trial by Sites *et al*[12] there was no statistically significant difference in the morphine consumption or pain scores between ITM and FNB group where SA was used for both groups. This trial reports more adverse effects in ITM group compared to FNB group but a slightly higher dose of ITM 0.25 mg was used. Tarkkila *et al*[13] compared ITM with continuous 3 in 1 femoral block in primary unilateral TKA patients and reported lower pain scores in ITM group. Our study involved use of 0.2 mg ITM with statistically significant lower pain scores and morphine consumption without any respiratory depression. Perhaps a large prospective trial with standardized drug regime and multivariate analysis may

be needed to prove superiority of ITM over FNB in this particular group of surgical patients.

From our analysis we conclude that 0.2 mg ITM with SA is more effective for first 24 hour postoperatively compared to single shot FNB with GA for primary unilateral TKA. Also, 0.2 mg ITM is safe, time saving and cost effective with better patient satisfaction compared to FNB.

## ACKNOWLEDGMENTS

We thank Ms Carmen Kam Jia Wen, research officer at "Clinical and Trial and Research Unit" (CTRU) at Changi General Hospital, Singapore for her statistical help.

## COMMENTS

### Background

Total knee arthroplasty (TKA) leads to considerable post-operative pain, which requires optimal control for early mobilization. Till date, varieties of techniques and drugs have been used to achieve this optimal pain control. Use of intrathecal morphine (ITM) with spinal anesthesia (SA) is extremely easy and can be time saving and cost effective. Also, femoral nerve block (FNB) is one of the easiest peripheral nerve blocks. In this study the authors have compared these two easy techniques for postoperative pain management after TKA.

### Research frontiers

Regional blocks are commonly used for pain management after TKA. Most recent studies are comparing femoral nerve blocks with adductor canal block and local infiltration techniques. This study compares use of ITM with SA and FNB with GA. In the past only three other studies have compared ITM and FNB, albeit both groups had undergone surgery under SA.

### Innovations and breakthroughs

In this study, 0.2 mg ITM with SA was more effective for first 24 hour post-operatively compared to single shot FNB with GA for primary unilateral TKA. In one previous study, which compared 0.1 mg ITM with SA and FNB with SA, pain scores and postoperative opioid consumption were lower in ITM group though statistically not significant. In another similar study, ITM group had more complications when a higher dose of 0.25 mg ITM was used. In their study using 0.2 mg ITM, lower pain scores and opioid consumption were statistically significant. This study also illustrates that use of adequate prophylaxis can prevent known complications of ITM.

### Applications

This retrospective analysis shows that 0.2 mg ITM with SA is more effective for first 24 h postoperatively compared to single shot FNB with GA for primary unilateral TKA. Perhaps a prospective trial with standardized drug regime and multivariate analysis in a large group of patients is required to prove their findings.

### Terminology

ITM: Intrathecal morphine; FNB: Femoral nerve block; SA: Spinal anesthesia; GA: General anesthesia; PONV: Postoperative nausea and vomiting; PCA: Patient controlled analgesia; NSAIDs: Non-steroidal anti-inflammatory drugs; VAS: Visual analogue scale.

### Peer-review

This retrospective analysis is worthy of publishing as it provides value clinical information for how pre-emptive analgesia could effectively prevent or mitigate postoperative pain.

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