**ISSN** 2218-6182 (online)

# World Journal of *Anesthesiology*

*World J Anesthesiol* 2015 November 27; 4(3): 49-90

Published by Baishideng Publishing Group Inc

WJA World Journal of Anesthesiology

A peer-reviewed, online, open-access journal of anesthesiology

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World Journal of Anesthesiology

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Four-monthly Volume 4 Number 3 November 27, 2015

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*World Journal of Anesthesiology*
**Volume 4 Number 3 November 27, 2015**

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NAME OF JOURNAL
*World Journal of Anesthesiology*

ISSN
ISSN 2218-6182 (online)

LAUNCH DATE
December 27, 2011

FREQUENCY
Four-monthly

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http://www.wjgnet.com

PUBLICATION DATE
November 27, 2015



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DOI: 10.5313/wja.v4.i3.49

*World J Anesthesiol* 2015 November 27; 4(3): 49-57
ISSN 2218-6182 (online)


REVIEW

# Zygapophysial joint pain in selected patients

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Author contributions: Klessinger S solely contributed to this paper; he wrote the complete manuscript.

Conflict-of-interest statement: No conflict of interest is declared by the author.



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Received: May 3, 2015
Peer-review started: May 7, 2015
First decision: July 30, 2015
Revised: September 2, 2015
Accepted: September 10, 2015
Article in press: September 16, 2015
Published online: November 27, 2015

## Abstract

The zygapophysial joints (z-joints), together with the intervertebral disc, form a functional spine unit. The joints are typical synovial joints with an innervation from two medial branches of the dorsal rami. The joint capsule and the surrounding structures have an extensive nerve supply. The stretching of the capsule and loads being transmitted through the joint can cause pain. The importance of the z-joints as a pain generator is often underestimated because the prevalence of z-joint pain (10%-80%) is difficult to specify. Z-joint pain is a somatic referred pain. Morning stiffness and pain when moving from a sitting to a standing position are typical. No historic or physical examination variables exist to identify z-joint pain. Also, radiologic findings do not have a diagnostic value for pain from z-joints. The method with the best acceptance for diagnosing z-joint pain is controlled medial branch blocks (MBBs). They are the most validated of all spinal interventions, although false-positive and false-negative results exist and the degree of pain relief after MBBs remains contentious. The prevalence of z-joint pain increases with age, and it often comes along with other pain sources. Degenerative changes are commonly found. Z-joints are often affected by osteoarthritis and inflammatory processes. Often additional factors including synovial cysts, spondylolisthesis, spinal canal stenosis, and injuries are present. The only truly validated treatment is medial branch neurotomy. The available technique vindicates the use of radiofrequency neurotomy provided that the correct technique is used and patients are selected rigorously using controlled blocks.

**Key words:** Zygappophyseal joint; Facet joint; Low back pain; Medial branch block; Radiofrequency neurotomy; Interventional pain therapy; Chronic pain



**Core tip:** This review emphasizes the importance of the zygapophysial joints (z-joints) as a pain generator. Taking the historic or the physical examination are not helpful in identifying z-joint pain. The prevalence of z-joint pain increases with age, and it often comes along with other pain sources. The focus is on the significance of z-joint pain in elaborated patient groups in which z-joint pain is clinically relevant but does not occur as an isolated and independent disease. Diagnostic methods and the treatment with radiofrequency neurotomy are discussed.

Klessinger S. Zygapophysial joint pain in selected patients. *World J Anesthesiol* 2015; 4(3): 49-57 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/49.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.49

## INTRODUCTION

The smallest functional motion consists of two vertebrae, all adjoining ligaments between them, and three joints. First, there is the interbody joint, which consists of the intervertebral disc and the vertebral endplates. The other two joints are the paired zygapophysial joints (z-joints), which are formed by the articulation of the inferior and superior articular processes of two adjacent lumbar vertebra. The nomenclature of the small joints of the vertebral spine is inconsistent. Facet joint is commonly used in North American literature to describe paired synovial joints between the posterior elements of adjacent vertebrae. The joints are also known as z-joints, zygapophyseal joints, apophysial joints, or posterior intervertebral joints. Because a facet is simply a small articular surface and, as such, pertains to any small joint, in this review the term z-joint is used.

The existence of pain deriving from the z-joints is discussed controversially. In the existing literature there is no support for the existence of a facet syndrome. There are no typical examination findings or diagnostic proofs to justify the term "syndrome". Z-joint pain is defined as pain originating from any structure essential to the function and the configuration of the lumbar facet joints, including the capsule, synovial membrane, hyaline cartilage surfaces, and bony articulations[1].

This review provides an overview about the clinical presentation and treatment of z-joint pain with emphasis on selected patients and diagnosis.

### *Prevalence*

The proposal that the lumbar z-joints might be a source of back pain had initially been communicated more than 100 years ago by Goldthwaith[2] in 1911. In 1933, the term "facet joint syndrome" was introduced[3]. With the implementation of successful operations of herniated discs by Mixter[4] in 1934, the focus was directed away from the z-joints and towards the intervertebral discs. The prevalence of zygapophysial pain is very difficult to specify. In the literature, studies with different prerequisites are found. In original prevalence studies the prevalence was 10%-20%[5]. Later studies reported prevalence rates of 27%, 31%, 38%, and 45%[6-9]. The recent investigation by DePalma *et al*[10] found a prevalence for z-joint pain of 31%. One reason for the incongruity between the different studies is the difference in the age of the groups studied. There is an increasing prevalence with a maximum of more than 40% up to age 70[10]. In patients with thigh pain, older age was even more predictive of z-joint pain with a predicted probability of more the 50% in 60-year-old patients and more than 85% in patients over 80 years old[11].

### *Anatomy*

Although the z-joints are small, they show the features typical of synovial joints[12]. This means the facets are enclosed by a capsule. The surface of the facets is covered by cartilage, a typical synovium, and even a meniscoid exists. The z-joints of the lumbar spine are innervated from the medial branches of the dorsal rami of the spinal nerves at the same level and from the level above. The medial branch of the dorsal ramus in the lumbar spine runs over the base of the transverse process at the junction of the superior articulating process (Figure 1)[13-15]. The lumbar dorsal rami have the same number as the vertebra from which they originate. In their course, these nerves traverse structures and innervate joints caudad the segment of origin[16]. Subsequently, each medial branch passes under the mamillo-accessory ligament[17]. This ligament is responsible for the consistent location. It can be large and sometimes ossified, particularly at lower levels[17]. Outside the ligament, the medial branch sends branches to innervate the z-joint, multifidus muscle, interspinal muscles, and the interspinous ligaments[18]. The z-joints are involved in all principal movements of the spine. Possible movements are axial compression/distraction, flexion/extension, axial rotation and lateral flexion. Horizontal translation does not occur as isolated movement[19].

### *Symptoms*

Pain originating from the z-joints results from noxious stimulation and is therefore a somatic pain. Z-joint pain is often associated with pain in the buttock or in the leg. However, in this case, it is a somatic referred pain and not a radicular pain. Referred pain occurs because of a misperception of the region of the signal that reaches the brain by a convergent sensory pathway[20]. Somatic referred pain is perceived deeply. It is diffuse and hard to localize and it is aching in quality[21]. Pain at the beginning of a movement is typical for joints. Therefore, the z-joints often hurt when moving from a sitting to a standing position or while sleeping when turning from one side to the other. Morning stiffness with difficulty to put on socks in a standing position and pain early in the morning that is relieved during the next hours and with walking will be reported often.

### *Diagnosis*

No historic or physical examination variables exist to identify a z-joint as the pain source[22,23]. Target joints can be recognized by the pain pattern, local tenderness over the area, and provocation of pain with deep pressure. The neurological examination is usually normal. Pain is the most common reason why patients undergo imaging of the spine[24], however, the the routine use of radiological imaging to diagnose z-joint pain is not supported by evidence in the literature[25-30]. The majority of

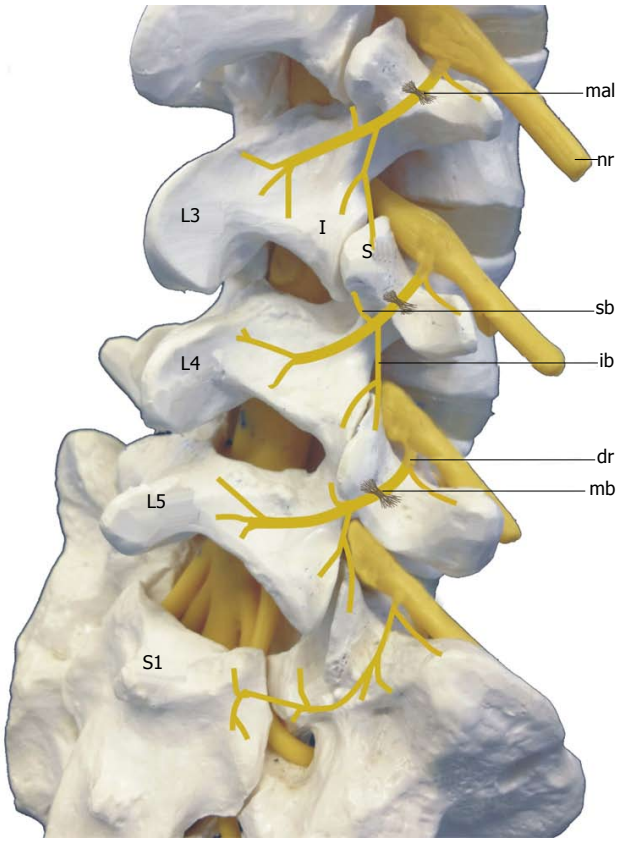


**Figure 1 Lumbar medial branch anatomy.** Left anterior oblique illustration (L3 to S1): Spinous processes. mal: Maillo-accessory ligament; nr: Nerve root; I: Inferior articular process; S: Superior articular process; sb: Superior branch from medial branch; ib: Inferior branch of medial branch; dr: Dorsal ramus; mb: Medial branch[13,14].

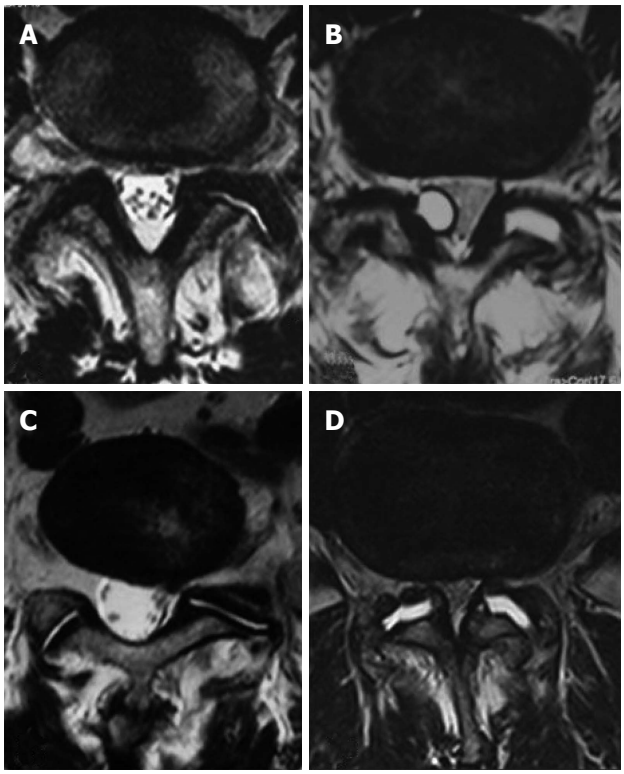


**Figure 2 Examples of magnetic resonance imaging findings concerning the zygapophysial joints.** A: Degenerative changes; B: Synovial cyst of the z-joint and increased joint volume; C: Asymmetric joint gap; D: Increased joint volume[13,14]. Z-joint: Zygapophysial joint.

clinical investigations testify no correlation between the clinical symptoms of low back pain and degenerative changes observed on radiological imaging, including radiographs, magnetic resonance imaging (MRI) (Figure 2), computed tomography (CT), single-photon emission computed tomography (SPECT), and radionuclide bone scanning[28-30]. Specifically, the association between degenerative changes in the lumbar z-joints and symptomatic low back pain remains unclear and is a subject of discussion[25-28].

The most accepted method[31] for diagnosing z-joint pain are controlled medial branch blocks (MBBs). MBBs are a diagnostic tool designed to test whether the pain stems from the z-joint because the medial branch innervates it[32]. They are the most thoroughly validated of all spinal interventional procedures[33,34]. The target nerve (medial branch of the dorsal ramus) is anaesthetized with a small volume of local anesthetic. The medial branch cannot be regarded as mediating the pain, if the pain is not relieved after a MBBs, this means the z-joint is not the pain source. A new suggestion about the pain source is necessary. If case of a positive answer, the pain source is recognized and a good chance of obtaining pain relief after denervation of the nerve is expected[35,36]. Single diagnostic blocks are not valid because they have an unacceptable high false-positive rate of 25%-45%[5-9,31]. To reduce the possibility of responses being false-positive, controlled blocks are mandatory[29]. Uncontrolled blocks or intra-articular blocks lack validity[31].

### *Therapy*

No specific conservative treatment for z-joint pain exists. Patients with z-joint pain are treated in the same way as patients with low back pain emerging from a different pain source. Guidelines only exist for radiofrequency denervation of the z-joints, published by the International Spine Intervention Society[16]. Radiofrequency denervation is the direct consequence after the diagnosis of z-joint pain has been validated by controlled MBBs and it is the only validated treatment for pain mediated by the medial branches[29]. Percutaneous radiofrequency neurotomy offers pain relief by denervation of the painful joints. It is a percutaneous therapeutic procedure in which a radiofrequency electrode is used to coagulate the medial branches of the lumbar dorsal rami, or the L5 dorsal ramus, in order to relieve back pain mediated by these nerves (Figure 3)[14].

The available data vindicate the use of lumbar medial branch neurotomy provided that the correct surgical technique is used and patients are selected rigorously using controlled blocks[16,31]. There are no data that vindicate any other technique[16]. If the criterion for a positive response to diagnostic blocks is raised to complete relief, some 56% of patients

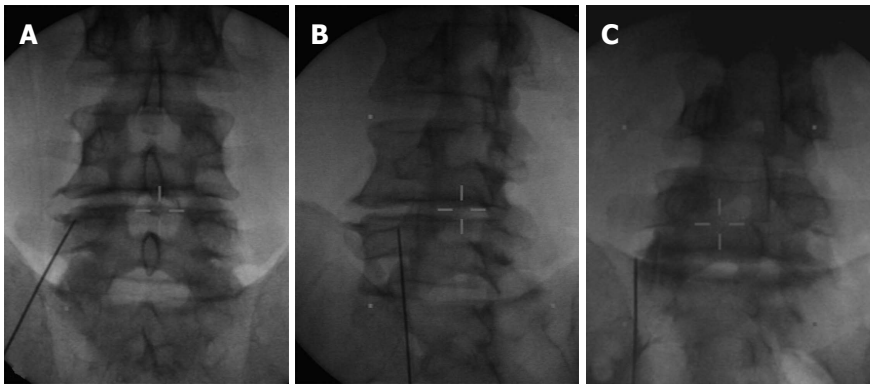


**Figure 3 Different views of an electrode placed for an L4 medial branch neurotomy.** A: Antero-posterior view; B: Corresponding oblique view; C: Antero-posterior view of an electrode placed for an L5 medial branch neurotomy[14].

obtain complete relief of pain[37]. They return to their normal activities, and the need for other health care is eliminated.

## SELECTED PATIENTS

Particularly well studied is z-joint pain in patients without comorbidities. In this group of patients, diagnostic standards can be applied best and success rates after a specific therapy can be measured. In this review, the significance of z-joint pain is elaborated in patient groups in which z-joint pain is clinically relevant but does not occur as an isolated and independent disease. It is thus expected that diagnostic and therapeutic methods are only partially successful. For the patients, this can nevertheless make a significant difference in their daily lives.

### *Degeneration*

During life, changes occur to the intervertebral disc and to the z-joints called spondylosis or osteoarthrosis. After the fifth decade, the subchondral bone of the z-joint gets thinner[38]. Severe or repeated pressure may result in erosions and focal thinning of the cartilage (Figure 4). These changes are not a disease per se but an expression of the morphological consequences of stress applied to the disc and the joints during life. The incidence of osteoarthrosis is just as great in patients with symptoms as in patients without symptoms[39,40]. Additional factors must be present to make the z-joints a pain source.

Z-joints are commonly altered by osteoarthritis. The arthritis is usually secondary to disc degeneration or spondylosis[41], but in 20% of cases it can be totally independent[42]. This condition is believed to be a possible cause of z-joint pain[43-46]. Inflammatory mediators, such as cytokines, prostaglandins, and neuropeptides, increase within the joint and the dorsal root ganglion in joint inflammation and arthritis[47-49]. Specifically, prostaglandin E2 has been identified as a key mediator of inflammation and amplified neuronal excitability[50-52].

Synovial cysts arise from the z-joint capsule of the lumbar spine (Figure 2B)[53]. They contain serous, gelatinous, or hemorrhagic fluid and are sometimes lined with synovium[54]. The development is related to degenerative spondylosis, segmental instability, and perhaps trauma[54,55]. They are a cause of back pain and radiculopathy, with z-joint degeneration being the most common cause for cyst formation[56].

A temporary one-sided load is often found in the context of knee or hip problems with appropriate gait disturbance or when walking with crutches. These patients often develop z-joint pain without structural changes. The reason is unusual strain or overuse of the joint. The treatment prognosis is good. Facet tropism (asymmetry of the facet angles) may have an association with degenerative changes in the spine, either as the cause of degenerative changes or as the result of abnormal loads produced by degeneration[57]. These degenerative changes can be a cause of back pain[57]. The clinical significance of facet tropism is not yet well proven[57-62].

### *Elderly patient*

Degenerative changes are more common in older age. The joints can be affected by osteoarthritis, which is believed to be a possible cause of z-joint pain[43-46]. Compared with other sources of low back pain (*e.g.*, discogenic pain or sacroiliac joint pain), z-joint pain becomes the most important pain source[11]. However, there is often an image of mixed pain of various causes. Especially in combination with discogenic changes, spinal canal stenosis and degenerative spondylolisthesis several pain sources might exist.

### *Spinal canal stenosis*

Patients with a spinal canal stenosis on the one hand have a symptomatology coming from the stenosis and the compression of the nerves in the dural sac. These symptoms are called claudicatio spinalis and are manifested in a restricted walking distance with pain, a sensory disturbance in the legs, or even neurologic deficits. On the other hand the most important reason for the development of a spinal canal stenosis is the

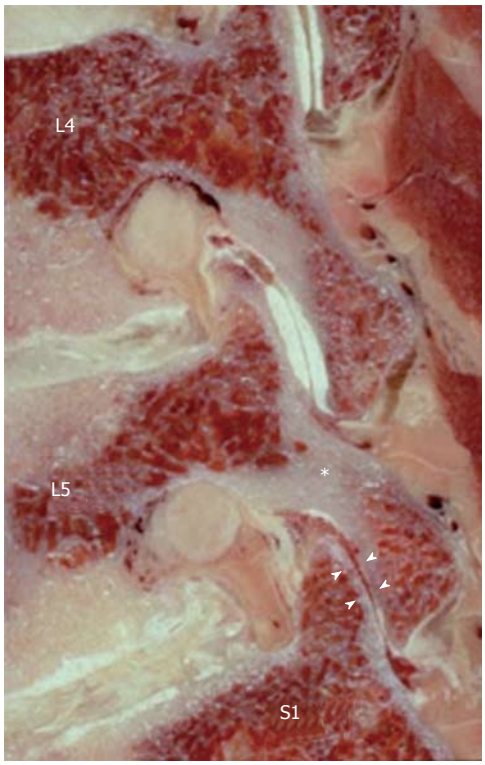


**Figure 4 Sagittal section through the neuroforamina of a severely degenerated lower lumbar spine of a 70-year-old man.** The z-joints are in a subluxated position due to the loss of segmental height. The pars interarticularis of L5 is being eroded superiorly by the inferior articular process of L4 and inferiorly by the superior articular process of S1 (*). Such pars erosion is a prerequisite for the development of degenerative spondylolisthesis. There is no cartilage in the L5/S1 z-joint (arrow heads). Z-joints: Zygapophysial joints.

destruction of the z-joints[63]. Therefore, patients suffer at the same time from pain deriving from the z-joints. Epidural steroid injections are commonly used to relieve symptoms caused by lumbar spinal stenosis[64,65]. Treatment of z-joint pain as described above, including radiofrequency neurotomy is an alternative for patients for whom back pain is prominent and for patients with high risk of bleeding[66].

### *Spondylolisthesis*

The loss of the normal structural support as seen in arthritis of the z-joints is the main local reason that probably leads to the development of degenerative vertebral slippage[67,68]. It seems to be obvious that morphological deformities of z-joints in the lumbar spine are an important cause of low back pain and segmental instability and a predisposing factor in the development of degenerative spondylolisthesis[69-71]. One of the most probable sources of pain related to degenerative spondylolisthesis are degenerated and subluxated z-joints and segmental instability which causes tension in the z-joint capsule and ligaments[67,70]. Spinal instability is often indicated by an increase of the joint volume[72], or synovial cysts associated with degenerative spondylolisthesis and z-joint osteoarthritis can be found[73]. An increased amount of fluid in the joint gap seen on axial MRI (Figure 2D) is significantly suggestive of spondylolisthesis[74].

It is well known that patients with degenerative spondylolisthesis also have sources of pain other than the z-joints[75]. In particular, the often additionally present spinal canal stenosis causes symptoms. The second pathology often interlinked with degenerative spondylolisthesis is disk degeneration[67,68], Spondylolisthesis is a characteristic example of concurrent pain sources in the same patient at the same time. The proportion by which the z-joints are involved in the complex symptoms is often difficult to diagnose[76].

Radiofrequency denervation is a rational treatment of low back pain in patients with degenerative spondylolisthesis because morphological deformities of the lumbar z-joints are a predisposing factor in the progress of degenerative spondylolisthesis[70], pathology of the z-joints is a important cause of low back pain within the lumbar spine[69]. An adequate pain reduction can be realized in 65% of the treated patients for a reasonable time[76,77].

### *Failed back surgery*

Z-joints are an important pain source not only in patients with chronic low back pain but also in patients after disc surgery[78-80]. Therefore, a specific therapy against z-joint pain is rational. Continued pain following lumbar spine surgery has been assumed to be secondary to multiple causes, including epidural fibrosis, acquired stenosis, sacroiliac joint pain, and z-joint pain[81-83]. It is difficult in post lumbar surgery syndrome to identify pain-generating structures[84]. The prevalence of z-joint pain in patients with post lumbar laminectomy syndrome is 32%. In patients after disc surgery, the prevalence of z-joint pain is 7% and 28% in patients with persistent back pain after surgery[79].

The reasons why the z-joints are involved even if the joint was untouched during the operation might be inflammatory processes, low-level trauma, changes in disc height, or stretching of the joint capsule[23]. The process of degenerative disc disease, particularly when enhanced by a herniated disc or discectomy, results in progressive loss of intervertebral disc volume and disc height and increased load to the joints, which might be a reason for pain[85]. Z-joint pain can be identified and treated with a radiofrequency neurotomy with a success rate of 58.8%[79] in patients after disc surgery.

After spinal fusion, z-joint pain can occur due to residual mobility in the index segment or in adjacent segments due to overload. Studies on the effectiveness of a specific joint therapy after spinal fusion do not exist.

### *Injuries*

Z-joint pain is expected to appear with repetitive, chronic strains as might be seen in the elderly, or after an acute incident such as tearing the capsule of the joint by extending it beyond its physiologic limits. This

theory is supported by clinical studies showing a higher prevalence of facet arthropathy in elderly patients[86-88] and numerous cases of lumbar facet arthropathy after high-energy trauma[89]. There is also evidence that cervical z-joints can be injured by whiplash injury and can become painful[90]. Studies using double-blind controlled MBBs found that the prevalence of pain deriving from one or multiple z-joints was between 54% and 60% amongst patients with chronic neck pain after whiplash; 27% of consecutive patients with neck pain and/or headache after whiplash had pain stemming from the C2/3 joint[91-93]. The level of symptomatic joints is consistent with the location foreseen by biomechanical studies: joints at C5/6 or C6/7 and at C2/3 are most commonly affected[94-96]. A placebo-controlled trial and several observational studies with long-term follow-up[97-102] have shown that percutaneous radiofrequency neurotomy can eliminate chronic neck pain after whiplash injury stemming from the z-joints in approximately 70% of treated patients.

Lumbar facet dislocation was reported in more than two dozen patients after rapid deceleration injuries[89,103-105]. The mechanism of injury in these cases is supposed to be a combination of hyperflexion, distraction, and rotation[89,103,106,107]. Both in biomechanical studies and in postmortem studies, capsular tears, capsular avulsion, subchondral fractures, intra-articular hemorrhage, and fractures of the articular process have been found[20,108-112]. Fractures of the z-joints cannot be detected on plain radiographs and might be too small to be seen in CT scans[111,112]. Lesions such as capsular tears cannot be detected by radiography, CT, or MRI. It may be that these lesions underlie z-joint pain[1].

## CONCLUSION

Z-joints meet all prerequisites to be a pain source. They are often involved in back pain and radiating pain and should not be underestimated. The prevalence of isolated z-joint pain increases with age. In addition, z-joint pain also appears in combination with other common spine diseases, such as disc degeneration, spinal canal stenosis, and spondylolisthesis. If the diagnosis is made with controlled MBBs, radiofrequency denervation is the only validated treatment for pain mediated by the medial branches.

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**P- Reviewer**: Ahmed AS, Charles B, DeSousa K, Sandblom G, Tufan M
**S- Editor**: Qiu S **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Anesthesiology

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DOI: 10.5313/wja.v4.i3.58

*World J Anesthesiol* 2015 November 27; 4(3): 58-65
ISSN 2218-6182 (online)


MINIREVIEWS

# Perioperative hypothermia: Causes, consequences and treatment

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Author contributions: All authors substantially contributed to conception and design of the review, drafting the article or making critical revisions related to important intellectual content of the manuscript, and final approval of the version of the article to be published.

Conflict-of-interest statement: All authors deny conflicts of interests with the presented material.



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Received: May 6, 2015
Peer-review started: May 8, 2015
First decision: June 3, 2015
Revised: June 24, 2015
Accepted: July 21, 2015
Article in press: July 23, 2015
Published online: November 27, 2015

## Abstract

Perioperative hypothermia, core temperature below 36.0 ℃, transpires due to disruption of thermoregulation by anesthesia coupled with cold exposure to procedural surroundings and cleansing agents. Although most publications have focused on thermoregulation disruption with general anesthesia, neuraxial anesthesia may also cause significant hypothermia. The clinical consequences of perioperative hypothermia are multiple and include patient discomfort, shivering, platelet dysfunction, coagulopathy, and increased vasoconstriction associated with a higher risk of wound infection. Furthermore, postoperative cardiac events occur at a higher rate; although it is unclear whether this is due to increased oxygen consumption or norepinephrine levels. Hypothermia may also affect pharmacokinetics and prolong postoperative recovery times and hospital length of stay. In order to combat perioperative hypothermia, many prevention strategies have been examined. Active and passive cutaneous warming are likely the most common and aim to both warm and prevent heat loss; many consider active warming a standard of care for surgeries over one hour. Intravenous nutrients have also been examined to boost metabolic heat production. Additionally, pharmacologic agents that induce vasoconstriction have been studied with the goal of minimizing heat loss. Despite these multiple strategies for prevention and treatment, hypothermia continues to be a problem and a common consequence of the perioperative period. This literature review presents the most recent evidence on the disruption of temperature regulation by anesthesia and perioperative environment, the consequences of hypothermia, and the methods for hypothermia prevention and treatment.

**Key words:** Body temperature regulation; Hypothermia prevention; Hypothermia; Hypothermia treatment; Intraoperative care



**Core tip:** Thermoregulation tightly controls core temperature to ensure optimal organ and enzymatic

function. Anesthesia disrupts normal thermoregulation and, when combined with patient exposure to a cold procedural environment, leads to hypothermia. However, hypothermia is not a benign issue. It is associated with postoperative complications including infection, bleeding, cardiac events, changes in drug metabolism, patient discomfort, and increased length of stay. Although multiple preventive strategies have been explored, their utility varies. This review explores the impact of anesthesia on perioperative hypothermia and the evidence for associated complications and outcomes. Preventative strategies are also examined and future directions for research are discussed.

McSwain JR, Yared M, Doty JW, Wilson SH. Perioperative hypothermia: Causes, consequences and treatment. *World J Anesthesiol* 2015; 4(3): 58-65 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/58.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.58

## INTRODUCTION

Normal core body temperature is approximately 37 ℃. As strict temperature control is important for normal organ, enzymatic, and cellular function[1], temperature control is tightly regulated by the body to within 0.2 ℃. This is referred to as the interthreshold range. Within this range, active methods of heating or cooling are not triggered. In addition, a set point temperature exists in which the body maintains steady changes in core body temperature (0.5-1.0 ℃) based on circadian rhythms. Temperature tends to be decreased during sleep and increased with physical activity[1,2].

Precise temperature regulation involves both the peripheral and central nervous systems through behavioral and autonomic triggers. Afferent signals for cold and hot sensations are transmitted *via* A-delta and C nerve fibers, respectively[2,3]. Sensory nerve fibers are thought to sense environmental temperature changes through skin projections[3]. These cutaneous "sensors" are recently characterized as transient receptor potential receptors located in both skin and spinal cord[4]. Temperature signals from the skin, spinal cord, deep abdominal/thoracic tissue, and other parts of the brain coalesce mainly within the anterior spinal cord and travel to the primary area of temperature regulation, the hypothalamus[2-4]. The hypothalamus then activates both behavioral and autonomic responses to temperature changes[3].

The human body tightly controls core temperature through a variety of mechanisms including behavioral modification, autonomic nervous system stimulation, surface skin sweating, and increased heat production *via* shivering and non-shivering thermogenesis[2]. Behavioral changes, such as a change in dress or moving out of the wind, are more influenced by skin temperature. Conversely, autonomic regulation actions including peripheral vasoconstriction or vasodilation are mostly dependent on core temperature[1].

## CAUSES OF PERIOPERATIVE HYPOTHERMIA

The human body loses heat to the atmosphere in four ways: radiation, conduction, convection, and evaporation[1,5]. Radiation is the infrared transfer of heat. Conduction involves heat transfer through physical contact with an object (*i.e.,* operating room table). Convection is the movement of heat based on air flow (*i.e.,* cold air blowing over body). Finally, evaporation refers to the loss of heat through sweat from skin or fluid loss from exposure of organs to the open atmosphere. The most significant heat loss, approximately 60%, occurs by radiation[2].

Multiple factors contribute to perioperative hypothermia development. Operating room temperature contributes to intraoperative hypothermia primarily through radiant heat loss. Although most operating rooms have in-room thermostats that are able to control the ambient temperature, disagreements about the optimal temperature settings may occur based on different levels of personal comfort, dress (surgical gowns), and other heat exposure (standing under hot lights)[5]. Additional heat loss occurs through conduction as the patient is positioned on the cold operating room table and through convection by laminar airflow. Further, operative cleansing solutions aid in heat loss through evaporation.

Under normal conditions, the human body would initiate mechanisms to preserve or create heat. However, anesthesia disrupts these homeostatic mechanisms. Concurrently, exposure to the cold procedural environment and vasodilation induced by general or regional anesthesia contribute to intraoperative hypothermia development[2,4].

### *General anesthesia*

Regardless of maintenance with volatile agents, dexmedatomidine, or propofol, general anesthesia impairs autonomic temperature control[2-4]. In fact, it may increase the interthreshold temperature range 5-20 fold, allowing temperatures to vary by 2-6℃.

After induction of general anesthesia, body heat redistributes from the central compartment to the periphery *via* vasodilation, causing heat loss to the environment[6]. Approximately 90% of this heat loss is through the skin *via* radiation and convection, with evaporation and conduction playing smaller roles[3]. This redistribution of heat mainly occurs during the first hour of general anesthesia and is responsible for about 80% of the core temperature drop; however, after induction redistribution continues for at least 3 h, making it the major contributor to intraoperative heat loss during general anesthesia[7]. Ventilation with dry gas, cutaneous heat loss, and cold surgical prep

solutions further contribute to overall intraoperative temperature decline[6,7]. After several hours, core temperature decline stops and autonomic-induced peripheral vasoconstriction occurs in an effort to bring heat back to the body's core. This is often referred to as the plateau phase which may occur 3-5 h into a general anesthetic[3].

### *Neuraxial anesthesia*

The mechanisms of heat loss with neuraxial anesthesia are similar to those of general anesthesia, but they also differ in important ways. Similar to general anesthesia, neuraxial anesthesia impairs autonomic temperature control[7]. Although redistribution during regional anesthesia decreases core temperature approximately half as much as during general anesthesia, it still remains the most important cause of core heat loss during the first hour. Unlike general anesthesia, there is not a temperature plateau phase with neuraxial anesthesia[8]. The blocked portion of the patient's body is unable to shiver or vasoconstrict regardless of the decrease in core temperature. For these reasons, a long case under neuraxial anesthesia may cause more heat loss than general anesthesia[9]. Neuraxial anesthesia also alters behavioral responses to hypothermia[10]. Patients do not feel cold despite being hypothermic, secondary to the peripheral vasodilation in the blocked extremities. Finally, core temperature is often not monitored with neuraxial anesthetics and accordingly hypothermia is not detected. Overall, hypothermia with neuraxial anesthesia may be as significant as with general anesthesia[11].

## CONSEQUENCES OF PERIOPERATIVE HYPOTHERMIA

Hypothermia affects over 60% of patients intraoperatively, and its effects are noteworthy[12]. It adversely impacts blood loss, infection risk, and cardiac events, potentially increasing length of hospital stay. It also slows anesthetic drug metabolism and may alter pharmacodynamics, thus contributing to increased post anesthesia care unit (PACU) recovery time.

### *Blood loss*

Studies that attempted to determine whether mild hypothermia leads to increased blood loss and transfusions have given inconsistent results[13]. A recent meta-analysis found that a median patient temperature of 35.6℃ resulted in increased blood loss (4%-26%) and an increased relative risk of transfusion (3%-37%)[13]. Notably, some studies included in the meta-analysis were from the 1990s when blood conservation techniques and transfusion thresholds may have been more liberal. However, in a recent large retrospective study of noncardiac surgeries published in 2015, transfusion requirements increased in proportion to the decrease in temperature and the increased duration of hypothermia[12].

Potential causes for increased blood loss include hypothermia-induced platelet dysfunction and coagulation cascade enzyme dysfunction. To evaluate coagulopathy, prothrombin time (PT) and partial thromboplastin time (PTT) were measured at different temperatures. For a given blood sample, PT and PTT increased from 11.8 ± 0.3 s and 36.0 ± 0.7 s to 12.9 ± 0.5 s and 39.4 ± 1.0 s, respectively, as the temperature of the sample decreased from 37 to 34 ℃[14]. Both PT and PTT continued to increase as temperature further decreased. It is important to note that blood samples are warmed to 37 ℃ prior to performing the lab tests[14]. Therefore, laboratory values may not reflect what is occurring physiologically in the patient.

### *Surgical wound infection*

Mild hypothermia has been associated with increased risk of surgical wound infection due to vasoconstriction and change in oxygen tension. At 34.5℃, thermoregulation leads to peripheral vasoconstriction[12]. When this occurs, oxygen delivery to subcutaneous tissues decreases impairing the strength of the collagen lattice that supports the healing scar[15,16]. Decreased oxygen delivery also impairs chemotaxis, phagocytosis, and antibody production by white blood cells and the immune system[17]. In patients undergoing colorectal surgery, the last intraoperative core temperature was strongly correlated with the incidence of postoperative wound infection. The hypothermic group (34.7 ± 0.6 ℃) had a 19% incidence of wound infections compared with 6% in the normothermic group (36.6 ± 0.5℃)[16].

### *Length of hospital stay and PACU recovery time*

Although most studies show that hypothermia contributes to increasing length of hospital stay and PACU recovery time, results are not consistent. A large study published in 1996 in colorectal surgery patients found that hypothermia (34.7 ± 0.6℃) at the end of surgery delayed patients' ability to tolerate solid food and suture removal by one day compared to patients with normothermia. Hospital length of stay also increased 20% (2.6 d) and length of stay was prolonged even after correcting for the increased risk of infection in the hypothermic group[16].

PACU discharge times are also impacted by hypothermia. Discharge from the PACU was observed to significantly increase by 40 min in hypothermic patients based on a modified Aldrete and Kroulik scoring system[18]. If discharge criteria included normothermia, then recovery was prolonged over 2 h[18].

### *Drug metabolism*

Mild hypothermia impairs temperature-sensitive enzymes that metabolize and clear anesthetic drugs, thus increasing their duration of action; the effect on potency differs depending on the drug. In animal models, moderate-severe hypothermia increases volatile anest-

hetic potency, thus decreasing minimum alveolar concentration (MAC)[19].

The duration of actions of midazolam, morphine, propofol, and several nondepolarizing neuromuscular blocking agents (*e.g.,* vecuronium, rocuronium, atracurium) are prolonged due to the pharmacokinetic effect of hypothermia. In nonsurgical healthy patients, midazolam clearance decreases 11.1% per 1℃ below 36.5 ℃[20]. The same decrease in clearance has been noted for vecuronium[21-24]. Additionally, mild hypothermia can cause a decrease in the twitch response even when neuromuscular blocking drugs are not given[25]. The twitch tension starts to decrease 16% per 1 ℃ once the temperature of the adductor pollicis muscle is below 35.2 ℃[26]. With moderate hypothermia to 30 ℃, morphine also has decreased potency, clearance, and volume of distribution; although, its concentration is elevated in the plasma and cerebral spinal fluid[27,28]. Notably, the efficacy of neostigmine and naloxone seems to be preserved during hypothermia[29].

### *Shivering and thermal discomfort*

If a patient is hypothermic, there is an increased incidence of thermal discomfort, oxygen consumption, vasoconstriction, and shivering[30]. Shivering is four times more dependent on core temperature than skin temperature[30]. However, core normothermia does not guarantee that shivering will not occur. During shivering, all patients are vasoconstricted[30]. In a study by Kurz *et al*[16], intraoperative vasoconstriction, measured by comparing forearm temperature with fingertip temperature, was noted in 74% of hypothermic patients *vs* 6% of normothermic patients. Postoperatively, hypothermic patients experienced persistent vasoconstriction for up to 6 h, decreased thermal comfort, and increased rates of shivering[16]. Although postoperative cutaneous warming decreases thermal discomfort, shivering intensity, and maximum oxygen consumption during shivering, it does not stop or affect the duration of shivering[30]. Fortunately, vasoconstriction and hypothermia usually resolve by postoperative day one[31].

### *Cardiac events*

The mechanism behind the increased postoperative cardiac risk with mild hypothermia is still unclear. Studies are inconsistent in determining whether the increased risk of myocardial infarction is due to shivering or stress hormones[32]. Although plasma catecholamine concentrations increase to three times normal in PACU, this finding has not been proven to be the cause[32]. To further this conundrum, hypothermia is thought to be cardioprotective during cardiopulmonary bypass and after cardiac arrest.

Although normothermia does not change the incidence of intra-operative cardiac events, it does reduce the postoperative risk by 55%[33]. In a study evaluating patients with high risk of coronary artery disease who had abdominal, thoracic or vascular surgery, those who were hypothermic had an increased incidence of postoperative cardiac events, including angina, ischemia, infarction, and cardiac arrest[33]. In the hypothermic group, cardiac events (6.3%) and ventricular tachycardia (7.9%) were significantly greater compared to the normothermic group (1.4% and 2.4%) respectively[33]. Similarly in the first 24 h following lower extremity revascularization surgery, hypothermic patients were significantly more likely to experience myocardial ischemia compared to normothermic patients (36% *vs* 13%, respectively)[34]. However, the incidence of intraoperative cardiac events was similar in the two groups[33]. In contrast, a significant difference in cardiovascular events or mortality was not noted between moderate hypothermic (33.3 ± 0.8 ℃) and normothermic patients undergoing intracranial aneurysm surgery[35].

The mechanism for the increased risk of myocardial ischemia in patients with mild hypothermia remains unclear. Shivering leads to increased metabolic demands but oxygen consumption alone has not proven to be the culprit[34]. Physiologic responses to hypothermia in nonsurgical patients include vasoconstriction[36] and sympathetic nervous system stimulation leading to increased epinephrine, norepinephrine, blood pressure, and heart rate[37,38]; however, stress hormones in surgical patients seem to respond differently. In a study by Frank *et al*[31] examining patients over 60 years old with two or more coronary artery disease risk factors and undergoing thoracic, abdominal, or lower extremity vascular surgery, hypothermic patients had significantly higher norepinephrine concentrations and arterial blood pressures but lower heart rates in the early postoperative period. While postoperative norepinephrine, epinephrine and cortisol concentrations increased in all patients, norepinephrine was significantly higher in the hypothermic group compared to the normothermic group[31]. Alternatively, during cerebral aneurysm surgery, intraoperative norepinephrine and cortisol levels decreased similarly in both the mild hypothermic and normothermic groups, while epinephrine had a significant decrease in the hypothermic group[39]. Intraoperative mild hypothermia also did not affect blood pressure when compared to normothermic patients. The difference between intraoperative and postoperative stress hormone levels may suggest that a time lag exists between stressful stimuli and hormone response; alternatively, anesthetics may attenuate the stress response and protect the myocardium. This would be consistent with the risk of myocardial infarction increasing and occurring postoperatively instead of intraoperatively.

## HYPOTHERMIA PREVENTION AND TREATMENT

Hypothermia treatment involves minimizing cold exposure while providing heat sources, such as heat transfer systems or pharmacologic agents, to equalize heat loss. Heat transfer systems may be passive or active.

Passive warming methods include passive insulation, environmental warming, and closed or semi-closed anesthesia systems. Active warming requires heat transfer to the patient through warmed fluids, circuit humidification, radiant heaters, forced or convective air warmers, infrared lights or circulating hot water systems. Alternatively, pharmacologic means may minimize heat loss through medications that decrease heat redistribution or through intravenous nutrients that stimulate metabolism and heat production. A combination of these methods is likely most effective in practice; however, prevention of hypothermia is likely a superior approach to treatment[40-42].

### *Passive warming*

Passive warming methods, including environmental heating and passive insulation, minimize but do not eliminate heat loss. The operating room temperature is the most critical factor influencing heat loss[43,44]. Heat loss increases as the difference between the skin and environment grows. Consequently, the simplest method to reduce heat loss is raising ambient temperature. Unfortunately, most operating room personnel find elevated temperatures intolerable making this approach impractical as a singular solution. Thermal insulation may be accomplished through mass or reflective covering. Reflective coverings prevent radiant heat loss by reflecting radiant heat back to the body. Mass coverings halt airflow between the covering materials. Surgical drapes and blankets are common examples, and covering patients with blankets is a standard practice. Heat loss may be reduced by as much as 33% with a single layer covering; however, prevention of heat loss is limited and multiple blankets are only slightly more effective than one blanket[45-47]. Unfortunately, effective covering of the body surface is often not feasible in the intraoperative setting making passive methods ineffective to prevent hypothermia.

### *Active warming*

Active warming is required in most situations to maintain normothermia. Methods include warming of intravenous fluids, cutaneous warming, pharmacologic vasoconstriction, and intravenous nutrients. Of these choices, cutaneous warming (*e.g.,* forced air warming, electrical resistance, circulating hot water device) is the most widely used[48].

**Cutaneous warming:** Likely the most common warming system, forced air warming is effective, safe, relatively inexpensive, easy to use[45,49], and superior to many other warming systems[50,51]. Forced air warmers were initially utilized to treat postoperative hypothermia before they were introduced for intraoperative warming. In this method, warmed air is forced into a receptacle, commonly a two-layer blanket, which lies in direct contact with a large surface area of the body. The forced air escapes through pores of the blanket material creating a warm microclimate over the area of contact. Heat transfer is dependent on both the amount of surface area covered and the temperature difference between the skin and blanket. Consequently, the effectiveness is dependent upon utilization of a properly shaped warming blanket, appropriate placement on the body, and selection of a high warming temperature.

The utility and consequences of forced air warmers have also been scrutinized. A recent, large retrospective study of over 58000 patients undergoing noncardiac surgery and utilizing forced air warmers found that 64.4% of patients were hypothermic 45 min after induction and 20% of patients continued to be hypothermic after 6 h of anesthesia[12]. Additionally, much discussion has occurred recently in regard to the potential for bacterial dispersion in the operating room by forced air warmers. However, studies examining contamination with and without forced air warmers did not find a difference[52,53].

Electrical resistance may also be used for heat production by sending an electrical current through a resistant polymer blanket or mattress[54]. These systems utilize conduction and are only effective when the warmed surface directly contacts the skin. This differs from forced air warmers, which create a carrier (air) for heat to travel from the warming blanket to the patient. Benefits of these devices include noiseless operation and slower temperature changes compared to the continuous supply of warmed air required with forced air warmers[54]. While the efficacy of electrical resistance warming blankets are similar to forced air warmers, they are expensive albeit reusable[54-56]. Additionally, an electrical mattress alone is insufficient to prevent hypothermia due to the negligible amount of body surface area contacting the operating table and the low amount of heat transfer[56,57]. Consequently, warming blankets (forced air warming or electrical resistance) must be utilized concurrently to prevent intraoperative hypothermia.

Since water has much greater heat capacity than air, it may be hypothesized that water systems would supply a great amount of heat. However, similar to electrical resistance systems, direct contact must be made with the skin. In addition, these devices have been found to be ineffective with posterior body warming alone[51]. As a result, water-warming blankets have been designed to wrap around the limbs[58] and trunk[59] depending on the surgical procedure. While anterior and posterior warming with water systems have demonstrated improved maintenance of normothermia in large upper abdominal surgeries compared to forced air warming alone, posterior water mattresses combined with anterior forced air warmers are comparable[60]. Further, thermal injury remains a concern for circulating water devices; especially mattresses[61]. Price and technological problems have also largely limited use of these systems.

The timing to initiate cutaneous warming is also important. Hypothermia prevention is less effective after anesthesia induction[40-42]. Warming patients prior to anesthesia induction substantially prevents the decrease

in core temperature caused by redistribution[62]. Pre-warming may also lessen intraoperative heat loss by increasing peripheral tissue temperature to resemble core temperature.

**Warming intravenous fluids:** Although heating intravenous fluids does not warm patients, it does assist in hypothermia prevention with administration of large volumes of Ⅳ fluids[63]. Multiple different systems and technologies have been developed to warm intravenous fluids and blood products. These include water baths, conductive warming with metal, countercurrent heat exchange, microwave technology, and forced-air warming. All systems provide a range of flow velocities and temperatures with built-in prevention technologies for excessive warming and air detection. However, while 42 ℃ is considered safe for blood administration[64], the safe upper limit is not well defined. Although reports have described heating intravenous fluids to 54 ℃[65], this practice is not studied and should not be utilized.

**Pharmacologic vasoconstriction:** Pharmacologic means to minimize heat loss caused by core-to-peripheral redistribution have been explored with a predominant focus on maintaining precapillary vasoconstriction. Induction with ketamine was associated with greater core temperatures throughout surgery compared to patients induced with propofol[66]. Similarly, phenylephrine infusion (0.5 μg/kg per minute) initiated immediately prior to general anesthesia induction was associated with a smaller reduction in core temperature compared to controls.

**Intravenous nutrients:** Administration of intravenous nutrients, such as amino acids and fructose, has been examined to maintain normothermia through endogenous heat production. Protein/amino acid administration increases whole-body heat content by 20% with a significant increase in body temperature in awake subjects[67]. Intravenous infusion of amino acids minimized core temperature decline and postoperative shivering following general anesthesia for open abdominal surgery[68]. Notably, the timing of amino acid administration was variable. In hip arthroplasty patients receiving neuraxial anesthesia, preoperative intravenous amino acid administration one hour prior to surgery elevated subjects' temperatures prior to spinal placement resulting in improved intraoperative normothermia with decreased blood loss compared to control patients receiving saline[69]. Oxygen uptake was also increased in subjects receiving amino acids. Intravenous fructose has also been examined. Patients receiving preoperative fructose infusions demonstrated greater core temperatures after anesthetic induction and throughout the study period[70]. Interestingly, improvement in normothermia was attributed to both amplified metabolic heat production and an elevated threshold for vasoconstriction.

## CONCLUSION

Despite the well-documented incidence of perioperative hypothermia, it continues to be a very common and avoidable anesthesia-related complication. Both general and neuraxial anesthesia impair normal physiologic temperature regulation. The consequences of perioperative hypothermia are significant and may include increased intraoperative blood loss, increased chance of surgical wound infection, increased length of PACU and overall hospital stay, decreased patient comfort, and increased rates of cardiac events. Although both passive and active cutaneous warming minimize heat loss and are commonly used strategies in most operating rooms today, these methods do not completely eliminate intraoperative hypothermia.

Few published studies characterize intraoperative temperature patterns. Rather, most publications have focused on postoperative temperatures and outcomes. Consequently, the impact of various normothermia strategies on intraoperative temperature patterns is not well elucidated. This is especially true in patients receiving neuraxial anesthesia, where temperature monitoring is often inconsistent or absent.

As intraoperative hypothermia may be difficult to prevent in many cases, future studies should further characterize intraoperative hypothermia development and the impact on outcomes. Intraoperative characterization should investigate the impact of both preventative strategies and anesthesia type. Postoperative outcome studies should examine the extent and duration of hypothermia and how it relates to negative perioperative outcomes.

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**P- Reviewer**: Afzal M, Ewers A, Spasojevic SD
**S- Editor**: Tian YL **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Anesthesiology

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DOI: 10.5313/wja.v4.i3.66

*World J Anesthesiol* 2015 November 27; 4(3): 66-72
ISSN 2218-6182 (online)


MINIREVIEWS

# Sugammadex: Role in current anaesthetic practice and its safety benefits for patients

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Author contributions: Copp MV and Barrett TF contributed equally to this work.

Conflict-of-interest statement: Copp MV has in the past received honoraria from MSD for serving as a speaker but none is related to this publication and MSD has not been involved in the writing of this article.



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Received: May 20, 2015
Peer-review started: May 22, 2015
First decision: July 10, 2015
Revised: July 30, 2015
Accepted: August 20, 2015
Article in press: August 21, 2015
Published online: November 27, 2015

## Abstract

Sugammadex has revolutionized anaesthetic management of reversal of neuromuscular block (NMB) by way of its unique mechanism of action encapsulating the amino steroid neuromuscular blocking drugs rocuronium and vecuronium. The cholinesterase inhibitors have significant pharmacological and clinical limitations whereas sugammadex allows predictable, safe and rapid reversal from any depth of blockade. The financial cost of sugammadex is significant. Many hospitals in the United Kingdom use clinical guidelines to direct best use of sugammadex in their institutions. Auditing the use of sugammadex provides useful information on which patients are benefiting from sugammadex. The clinical benefits of sugammadex are well understood. No patient should now be subjected to the danger of post-operative residual curarization. Versatility in the ability to reverse NMB has brought opportunities to the anaesthetist in the management of rapid sequence induction using high dose rocuronium with the knowledge that safe reversal of NMB is now possible in the unlikely event of a "can't intubate can't ventilate" situation. Do we still need suxamethonium to be available? The nature of surgery continues to evolve with ever-increasing enthusiasm for minimally invasive laparoscopic techniques. There is evidence to support using a deeper level of NMB to improve the working space and operating conditions in laparoscopic surgery. It is now possible to maintain a deep level of NMB right up until the end of surgery with no concerns about the ability to effect safe reversal of NMB. Vigilance about the possibility of allergic sensitivity to sugammadex needs to be maintained. The increased usage of rocuronium has the potential for rocuronium-induced anaphylaxis. Conversely, there is a potential role for sugammadex in the treatment of rocuronium anaphylaxis. Clinicians who have used sugammadex are struck with the quality of recovery seen in their patients. It is important that the economic implications of the use of sugammadex are fully understood. This article considers the current role of sugammadex in clinical practice outside of routine reversal of NMB and discusses how the addition of sugammadex to the anaesthetic armamentarium brings safety benefits for patients.

**Key words:** Sugammadex; Neuromuscular block; Clinical benefits; Patient safety; Cost benefit

**Core tip:** Sugammadex is a new drug to reverse neuromuscular blockade. Its unique mechanism of action has revolutionized the management of neuromuscular block. For the first time anaesthetists have the ability to reverse safely and predictably from any level of neuromuscular blockade transforming its clinical management. Postoperative residual curarisation can be eliminated bringing significant safety benefits to patients. Sugammadex is expensive and anaesthetists need to use it in a cost effective way for appropriate patients and anaesthetic techniques. Clinical guidelines can help in ensuring that sugammadex is used responsibly in current clinical practice.

Copp MV, Barrett TF. Sugammadex: Role in current anaesthetic practice and its safety benefits for patients. *World J Anesthesiol* 2015; 4(3): 66-72 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/66.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.66

## INTRODUCTION

Sugammadex was licensed for use by the European Medicines Agency on 29 July 2008 and launched for use in the United Kingdom in November 2008. It is now available for use throughout Europe, Asia, Japan, Australia and New Zealand. The anticipated launch of sugammadex in the United States has been put back after the Food and Drug Administration (FDA) cancelled its meeting in March 2015 of the Anesthetic and Analgesic Drug Products Advisory Committee, which was planned to discuss the resubmission of the New Drug Application for sugammadex.

MSD United Kingdom estimate that in the United Kingdom 70000 patients were given sugammadex last year and it is estimated that globally in excess of 8.9 million patients have been exposed to sugammadex without significant reported adverse events showing it to be a safe, effective and important new drug[1].

## CLINICAL ROLE OF SUGAMMADEX

The original clinical trials evaluating sugammadex clearly demonstrate that it achieves faster and more predictable recovery of neuromuscular block (NMB) from a moderate level of NMB as defined by a return of two twitches (T2) of the train of four (TOF) count and from a deep block of NMB at the level of a post tetanic count (PTC) of 1-2. The dose dependent response of sugammadex has also been shown to be effective in reversing safely from a profound level of block immediately after administration of an intubating dose of 1.2 mg/kg of rocuronium as used in a rapid sequence induction (RSI) of anaesthesia[2].

At the launch of sugammadex, emphasis was placed on the rapid and predictable reversal of NMB as compared to reversal with traditional cholinesterase inhibitors. The expectation was that sugammadex might universally replace the cholinesterase inhibitors in everyday clinical practice. The issue for the majority of clinicians and healthcare providers was the financial cost of sugammadex. In the United Kingdom such was the concern about the introduction of sugammadex on pharmacy and operating theatre budgets that many hospitals struggled to get formulary approval. In our own institution a guideline (Table 1) was written in an effort to inform usage in a rational manor to take advantage of the clear clinical benefits whilst trying to contain the likely adverse effect on the operating theatre budget[3].

We audited the use of sugammadex for the first six months after it became available. The aim of the audit was to check adherence to our guidelines and to give a quantitate figure for the overall use of sugammadex to inform effects on the operating theatre pharmacy budget.

In our institution approximately 18000 general anaesthetics are given per annum of which 15% use an NMB. In the first six months of sugammadex being available the drug budget for reversal agents (neostigmine + glycoplyrolate + sugammadex) increased by 60%. In the context of the total theatre pharmacy budget for our institution the overall increase in this budget was less than 1%. This is a reflection of the fact that conventional reversal (neostigmine + glycopyrrolate) is so inexpensive.

The clinical findings of the audit showed that 30% of cases where sugammadex was administered there was a desire to avoid the side effects of neostigmine, in particular the potentially detrimental effect of a tachycardia in patients with known ischaemic heart disease. Sugammadex was used in 28% of cases to help ensure complete reversal of NMB in morbidly obese patients undergoing non-bariatric surgery (at the time of the audit our institution did not have a Bariatric Surgery programme). Sixteen percent of cases were ear nose and throat cases where deep NMB was required right up until the end of surgery. Sixteen percent of cases involved a need to provide optimal surgical conditions with deep NMB up to the end of surgery during laparoscopic surgery. Five percent of cases were to reverse patients with a known difficult intubation in an attempt to avoid airway compromise from any element of residual NMB at extubation. Five percent of cases were ASA 3/4 patients undergoing emergency surgery where it was considered essential to avoid any potential element of residual block that would be likely to significantly compromise patients in the post anaesthesia care unit (PACU).

Most hospitals in the United Kingdom have subsequently used a guideline to help facilitate introduction of sugammadex into clinical practice. It is accepted that morbidly obese patients are at increased risk of postoperative anaesthesia related complications. In

**Table 1 Suggested guideline for use of sugammadex**

| **Sugammadex is not to be prescribed for routine reversal from moderate NMB (TOF count > 2)** |
|---|
| Clinical situations where avoiding the use of neostigmine and glycopyrrolate potentially gives significant safety benefits to patients, *e.g.*, avoidance of tachycardia/tachyarrthymias in patients with ischaemic heart disease and/or atrial fibrillation. Avoidance of potential bronchospasm in patients with brittle asthma |
| Concern about residual neuromuscular block (after rocuronium or vecuronium) post-operatively in patients with airway difficulty or respiratory insufficiency that have already been reversed with a max 5 mg dose of neostigmine |
| Reversal from deep neuromuscular block that would otherwise waste 30 min of theatre time if waiting for a TOF count of 2 to use neostigmine reversal, *e.g.*, when a large dose of rocuronium has been used to provide deep neuromuscular block for a short surgical procedure or the surgery has finished earlier than predicted |
| In morbidly obese patients where there is a concern about the potential for residual neuromuscular blockade following reversal of NMB drugs |
| Emergency reversal of rocuronium (1.2 mg/kg) using the sugammadex rescue pack (16 mg/kg) after failed intubation at RSI |

NMB: Neuromuscular block; TOF: Train of four; RSI: Rapid sequence induction.

particular, morbidly obese patients undergoing non-bariatric surgery with a history of sleep apnoea are at risk of airway complications in the PACU. It is essential in this group of patients that the muscles of the upper airway, which are some of the most sensitive to the presence of a NMB and hence post-operative residual curarization (PORC), have achieved complete reversal at the time of extubation[4,5]. Sugammadex would seem to be ideally suited to reversal from NMB in this high-risk group of patients. Anaesthetists practising bariatric surgery are debating the use of a deep block technique compared to moderate block with remifentanil and further evidence is required to support the routine use of sugammadex in bariatric surgery.

There is clear evidence that critical respiratory events occur in the PACU as a result of PORC as shown by Murphy and colleagues[6]. In our institution we have recently published a case report of a patient who developed stridor in the PACU as a result of PORC which, when recognized as such, was swiftly and effectively resolved by sugammadex administration[7].

## RSI AND CAN'T INTUBATE CAN'T VENTILATE

The traditional purist RSI using thiopentone and suxamethonium alone to induce anaesthesia and achieve endotracheal intubation is less commonly performed in United Kingdom clinical practice today. More often a modified form of RSI is carried out substituting thiopentone for propofol or supplementing the core induction medications with short acting opioids for dose sparing effect and in an attempt to obtund the laryngeal reflex during airway manipulation.

More recently, high dose rocuronium (1.2 mg/kg) has been shown to produce identical intubating conditions as suxamethonium[8]. Given the numerous side effects and contra-indications to suxamethonium this has become an increasingly attractive alternative. However, the use of rocuronium confers an intermediate duration of neuromuscular blockade (60-90 min)[9]. Prior to the introduction of sugammadex this would preclude the option of neuromuscular blocking agent reversal and waking a patient up in the event of a failed intubation, or indeed a Can't Intubate Can't Ventilate (CICV) scenario. However, with its potential to rapidly reverse a deep NMB, the question remains as to whether sugammadex has transformed the safety of a rocuronium based RSI.

Sugammadex reversal of profound NMB has been shown to be significantly faster than spontaneous recovery from suxamethonium[10]. Paton *et al*[11] reported on the successful use sugammadex after induction in a patient with airway difficulties. The key to a successful clinical outcome is early recognition of the CICV situation and administration of the appropriate dose of sugammadex (16 mg/kg) to reverse the intubating dose of rocuronium. It should be noted however, that the decision time to use sugammadex and its preparation in an emergency situation might cause significant delay in achieving full NMB reversal. Bisschops *et al*[12] (2010) demonstrated in simulation the extent of this delay and raise the concern that this may increase patient morbidity and mortality. If sugammadex is to be considered for CICV scenarios it must be readily available to be drawn up and immediately administered. In our trust we have put together an emergency reversal rescue pack stored in emergency theatres. It consists of three 500 mg ampoules of sugammadex, sufficient to recover a 93 kg patient that can be given promptly whilst exact doses are calculated and further sugammadex given as needed.

Individual experience must also be considered in the emergency use of sugammadex. Following its introduction, a number of hospitals in the United Kingdom only made sugammadex available in the theatre for the emergency treatment of a failed intubation. An individual poll conducted by the author at one such hospital found that no anaesthetist had actually ever used sugammadex. The concept that clinicians should use an unfamiliar drug in a difficult and potentially life-threatening situation could be questioned and may be criticised in the event of a poor clinical outcome. It follows that it could be considered unreasonable of an anaesthetist to use rocuronium for an RSI if they have no previous experience of using sugammadex in their own clinical practice.

Finally, we should perhaps be wary of becoming com-

placent with the availability of sugammadex in difficult airway trolleys. Mendonca warns of the risks of relying on sugammadex as a rescue plan in cases of anticipated difficult airway where awake tracheal intubation remains the gold standard[13]. The presence of sugammadex should not be a substitute for thorough pre-operative assessment of the airway, anticipation of difficulty and the presence of well thought out plans for management and back up.

## THE END OF SUXAMETHONIUM?

The arrival of sugammadex suggested that it would remove the need for suxamethonium[14]. Indeed the Difficult Airway Society guidelines are currently under review, due for publication in late 2015, and are likely to propose that rocuronium may be better than suxamethonium for RSI[15]. The question has been posed as to whether the availability of sugammadex will bring about the removal of suxamethonium from the anaesthetic drug cupboard. This issue was debated by Professor Mirakur RK and the author at the Annual Meeting of the British Association of Day Surgery[16]. It was agreed that whilst suxamethonium theoretically could be substituted by a rocuronium and sugammadex technique most clinicians feel uncomfortable not having access to suxamethonium, despite its considerable array of clinical side effects, in their clinical practice.

## DEEP NMB (PTC 1-2)

Sugammadex provides the anaesthetist for first time ever the ability to safely reverse from any level of NMB. This means that NMB could be maintained right up till the end of surgery without fear of having to prolong anaesthesia whilst waiting until the return of two twitches of the TOF to allow reversal with neostigmine and also fear of putting the patient at the potential risk of PORC.

Laparoscopic surgery is one area where the ability to maintain a deep level of block can bring safety benefits to the patient by improving intraoperative conditions for the surgeon. Over the last decade there has been a significant increase in the number and types of surgery that can be performed laparoscopically. The combined aims of the surgeon and anaesthetist are to do no harm, practice safe surgery, and produce an enhanced recovery for the patient. Major bowel surgery and the majority of gynaecological surgery are now routinely being performed using a laparoscopic technique. Avoiding large abdominal incisions brings real benefits to patients in terms of enhanced recovery.

The anaesthetist has a key role to play in assisting to provide optimal operating conditions for the surgeon right up until the end of surgery. There is evidence that provision of deep NMB can improve the operating conditions for surgeons, in particular the working space in laparoscopic surgery, with improved outcomes for patients[17,18]. In summary a deeper block prevents sudden unexpected patient movement, increases the working space, lowers intra-abdominal pressure and may reduce postoperative pain[19-21].

However, the place for deep NMB in laparoscopic surgery has been questioned with regard to the substantial economic considerations of maintaining deep block as compared to a less intensive block of TOF 1-3. Further evidence is required to ascertain if deep block contributes to better patient outcomes and truly improves surgical operating conditions[22].

## HYPERSENSITIVITY TO SUGAMMADEX

One of the concerns consistently preventing approval of sugammadex by the United States FDA regards the potential risk of drug-induced hypersensitivity reactions. Case reports of anaphylaxis following sugammadex administration with confirmatory skin prick testing certainly exist in the literature[23,24]. A recent review article by Tsur and Kalansky[1] (2014) examined these reports in more depth. Of the 15 cases that they identified during a thorough search of the literature 11 underwent skin prick testing and 10 of these were proven to develop sugammadex induced hypersensitivity. Based on these cases they conclude that hypersensitivity reactions to sugammadex usually occur within 5 min of its administration with the appearance of a rash, hypotension and tachycardia being the most frequently shared signs. Of note, all of the patients during this review survived and in the majority of cases there had been no previous exposure to sugammadex. This raises the possibility that patients may have been previously sensitized by cyclodextrins found in food or cosmetics and that previous exposure to the drug itself is not a pre-requisite for hypersensitivity.

Despite the existence of reports of hypersensitivity, sugammadex use appears to be well tolerated and there remain no reports in the literature of deaths associated with its use[9]. Indeed, cyclodextrins are considered to be a relatively inert group of medicines and the doses of sugammadex used clinically are low in comparison to other medicinal products that contain these substances[9]. Current estimates of incidence of hypersensitivity reactions are less than 1%[25]. Ultimately, as with any medication that we administer, we should remain vigilant to the possibility of reaction and hypersensitivity and to have clear guidelines to manage such an event.

## SUGAMMADEX IN THE MANAGEMENT OF ROCURONIUM INDUCED ANAPHYLAXIS

Conversely there has been some interest in the role of sugammadex in the management of rocuronium induced anaphylaxis. An allergic reaction to rocuronium is one of the most common causes of anaphylaxis in anaesthesia[9,26]. With the availability of sugammadex it

is foreseeable that there will be an increase in the use of rocuronium as a muscle relaxant of choice. Consequently there may be a rise in the number of cases of rocuronium-induced anaphylaxis. If sugammadex has a role in the management of this potentially life-threatening emergency then its presence in the anaesthetic cupboards can be further justified.

Sugammadex binds rocuronium. Studies have demonstrated that once encapsulated, a rocuronium-sugammadex complex is formed and the epitope of the rocuronium molecule is concealed, preventing its role in facilitating further allergic reaction[27,28]. Current evidence in clinical practice remains at a case report level. Most of these describe an improvement in clinical condition following the administration of large doses of sugammadex immediately, or soon after the recognition of rocuronium induced anaphylaxis. Once an allergic process and mast cell activation have been triggered it is unlikely that encapsulation of the rocuronium will affect the anaphylactic cascade[9]. Despite this, there have been cases where sugammadex has appeared to improve clinical condition even 10 min after rocuronium anaphylaxis, which is more difficult to explain biochemically[29,30]. Of course, sugammadex is only one of a number of treatments given in attempt to attenuate the anaphylactic process and without further evidence it should not be considered a single therapy in itself, however, it's role does appear to be expanding further than first thought.

## QUALITY OF RECOVERY

Clinicians with wide clinical experience of sugammadex universally remark on the enhanced quality of recovery of their patients in the PACU who have had NMB reversed with sugammadex. It is difficult to objectively measure the "quality" of recovery from anaesthesia but why do patients who have been reversed with sugammadex subjectively seem to have a superior recovery?

One explanation put forward is the change in excretion of rocuronium. During spontaneous recovery, rocuronium is taken up by the liver and excreted in the bile with no metabolism. After sugammadex reversal, rocuronium will be excreted as a complex with sugammadex *via* the glomeruli in the kidney. As a result, the uptake mechanism in the liver does not have to deal with rocuronium. If another drug or drug metabolite is also removed *via* this liver uptake mechanism, the clearance of that drug will be improved. This hypothesis needs further evaluation. Alternatively, it could simply be that the rapid and complete restoration of muscle tone followed by activation of muscle spindles which results in activation of the arousal centre in the brain. One would expect to see changes in the electroencephalogram if this hypothesis was correct but this has yet to be clinically evaluated. After conventional reversal up to 70% of the NMJ receptors may still be occupied by NMB but still produce sufficient recovery of a TOF to 0.9 indicating a satisfactory clinical recovery[31]. When 100% of receptors are free of NMB following complete removal of rocuronium the increase in muscle tone and muscle spindle activity may contribute to the appearance of enhanced well-being and a better quality of recovery whilst patients are in the PACU.

## ECONOMIC CONSIDERATIONS AND COST BENEFIT

In all healthcare environments the cost effective use of resources is paramount. The efficient use of the operating theatres and the PACU is an essential component of the cost effectiveness in any healthcare system. The debate that sugammadex brings economic efficiencies by increased case turnover in the operating room with reduced length of stay in the PACU will depend on the model of healthcare provision being utilized. It is clear that patients who are not fully recovered from NMB in the PACU have a delayed recovery room discharge[32].

There is an ever-increasing drive to improve theatre efficiency and facilitate rapid turnover between patients. Although "anaesthetic time" is often a relatively short part of the overall theatre time for each patient, certain operating lists can provide particular challenges for anaesthetists. Ear nose and throat and thoracic bronchoscopy surgery lists for example, where deep NMB is mandatory to enable surgical manipulation of the airway but with unpredictable, and often short, surgical time have traditionally proved difficult to manage efficiently for the anaesthetist. The side-effects of suxamethonium make it unattractive in these instances despite its rapid onset and offset, mivacurium remains unpredictable and other NMB require a certain timeframe before conventional cholinesterase reversal may be considered.

Short acting opioids such as alfentanil and remifentanil certainly have a role in facilitating such cases, however, they too confer side effects and alone may fail to achieve optimal surgical conditions. Sugammadex allows deep NMB with rocuronium that can then be completely reversed regardless of the duration of surgery. For this reason, in our Trust one of the agreed indications for sugammadex use is reversal from deep NMB that would otherwise waste 30 min of theatre time if waiting for a TOF count of 2 before administering neostigmine reversal (Table 1). The guideline relates to when a dose of rocuronium has been used to provide NMB for a surgical procedure where the surgery has finished earlier than predicted.

The clinical and cost effectiveness of sugammadex for the reversal of muscle relaxation after general anaesthesia in United Kingdom practice following routine and rapid induction of NMB was evaluated by Chambers *et al*[33] who concluded that sugammadex may be a cost-effective option compared with neostigmine+glyco pyrrolate for reversal of moderate NMB. There remain, however, considerable uncertainties about whether the full benefits of sugammadex can be realised in clinical

practice.

The economic benefits of sugammadex depend upon the funding processes of the healthcare system within which it is being used. Paton *et al*[34] have suggested there may be some economic benefit to its use. The reality for most hospitals in the United Kingdom is that it has been a challenge getting sugammadex on to the hospital formulary. The difficulties are compounded depending on whether institutions take a macroeconomic view on budgets where it is accepted that in comparison to overall theatre costs, currently approximately 30 Euros/min, the costs of anaesthesia are small compared to the overall theatre costs. Some institutions take a micro economic view where drug costs are isolated, easy to calculate and more difficult to justify. Savings in theatre turnover time, increased productivity and reduced length of stay in recovery may well offset the cost of using sugammadex in individual cases. Certainly if the use of sugammadex helps avoid a clinical crisis with potential significant morbidity or to prevent an ICU admission then the use of sugammadex can be justified[35].

In practice we have not seen the universal uptake of sugammadex to replace cholinesterase inhibitors simply because the impact upon healthcare budgets would be prohibitive. Anaesthetists are generally cost conscious and although the cost of anaesthesia is small in relation to the resource utilized by our surgical colleagues the cost of drugs is easy to quantify and measure. This has meant that most anaesthetists will use sugammadex for selected cases only. In our own institution the guideline described exists to direct use of sugammadex, which is audited and reviewed on a regular basis.

## CONCLUSION

The arrival of sugammadex presented the opportunity to change the practice of anaesthesia[36]. Sugammadex is a significant addition to the anaesthetic armamentarium enabling effective use of and safe recovery from the use of neuromuscular drugs when used as part of the classic anaesthesia triad of hypnosis, analgesia and muscle relaxation.

However, recognizing the reality of the cost implications of a blanket replacement of neostigmine + glycopyrrolate with sugammadex has lead clinicians to look carefully at how best to use this novel drug. Guidelines to direct use have helped to bring sugammadex onto hospital formularies.

The potential benefits of using sugammadex to avoid the well-known side effects of the conventional reversal agents in patients with significant clinical comorbidities are easily understood. The ability to provide a deep level of NMB for short periods of time without fear of an inability to reverse at the end of surgery is suited for certain surgical procedures. There is a belief that provision of a deeper level of block in particular for laparoscopic surgery has clinical benefits improving the operating conditions for surgeons and outcomes for patients but there needs to be further evidence to support this idea.

Sugammadex is a key rescue component of an RSI technique using high dose rocuronium in the rare scenario of a CICV where anaesthetists need to be familiar with its use. However, it would appear that we are not about to see suxamethonium disappear from the anaesthetic drug cupboard just yet. Finally, PORC in the recovery room although rare can be dealt with effectively in patients who have had a full dose of conventional reversal and the option of just waiting for the block to wear off consigned to history.

We suspect that the majority of anaesthetists in busy everyday clinical practice would welcome the chance to replace neostigmine universally with sugammadex but, with the ever-increasing pressure on healthcare budgets globally, this is highly unlikely to happen until sugammadex becomes more affordable.

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**P- Reviewer**: Armendariz-Buil I, Shorrab AA
**S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Jiao XK

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DOI: 10.5313/wja.v4.i3.73

*World J Anesthesiol* 2015 November 27; 4(3): 73-82
ISSN 2218-6182 (online)


MINIREVIEWS

# Swine model in transplant research: Review of anaesthesia and perioperative management

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Conflict-of-interest statement: None.



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Received: June 22, 2015
Peer-review started: June 27, 2015
First decision: July 27, 2015
Revised: September 18, 2015
Accepted: October 16, 2015
Article in press: October 19, 2015
Published online: November 27, 2015

## Abstract

Pigs are one of most common animal species to be used in biomedical models due to their many anatomical visceral similarities with humans, particularly with regards to transplantation. Despite this use, in many of the researches in which pigs are selected for transplantation, the anaesthesia used is an adaptation of human anaesthesia and presents some limitations such as a reduced analgesia a limited control in perioperative period. In this review we show some of the most important conditions in the preanaesthetic management and of swine as well as we review of anaesthetic protocols for the most common types of swine model of transplantation.

**Key words:** Swine; Anesthesia; Transplantation; Animal model; Perioperative management



**Core tip:** Swine is a common model in research, especially in transplantation studies. A correct management and anaesthesia as well as knowledge of the different protocols in pigs are useful in performing these researches.

Morgaz J, Navarrete R, Granados MM, Gómez-Villamandos RJ. Swine model in transplant research: Review of anaesthesia and perioperative management. *World J Anesthesiol* 2015; 4(3): 73-82 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/73.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.73

## INTRODUCTION

Pigs are one of most common animal species used in biomedical models due to their many anatomical visceral similarities with humans, particularly with regards to metabolic or cardiovascular diseases and for liver, lung or heart transplantation[1-4]. These similarities have meant that pigs have become a potential species in xenotrasplantation in primates species[5-7]. Despite this resemblance, different anatomical and physiological aspects should be considered in order to perform a successful anaesthesia technique in swine, especially considering that in these researches major surgical procedures are usually performed. In

**Table 1 Normal cardiorespiratory parameters of adult and healthy pigs during anaesthesia**

| Parameter | Range | Parameter | Range |
|---|---|---|---|
| Heart rate (beats/min) | 50-100 | Temperature (℃) | 36-38 |
| Respiratory rate (breaths/min) | 10-20 | Haemoglobin (g/dL) | 11-16 |
| Systolic arterial pressure (mmHg) | 80-140 | Et $CO_2$ (mmHg) | 40-45 (mechanical ventilation) |
| Diastolic arterial pressure (mmHg) | 60-120 | Arterial pH | 7.38-7.50 |
| Mean arterial pressure (mmHg) | 40-70 | $PaO_2$ (mmHg) | > 70-80 |
| Cardiac output (mL/kg per minute) | 60-140 | $PaCO_2$ (mmHg) | 35-50 (mechanical ventilation) |

$EtCO_2$: End-tidal of carbon dioxide; $PaO_2$: Partial pressure of oxygen; $PaCO_2$: Partial pressure of carbon dioxide.

addition, the perioperative care and management of pigs should be considered. In Table 1 are shown normal cardiorespiratory parameters of adult pigs during anaesthesia.

## PERIOPERATIVE CARE AND GENERAL CONSIDERATIONS

As with other animals of research, an acclimatization period of 5-7 d prior to anaesthesia is necessary to reduce the depressant effect of transport or stress, which could alter the anaesthetic effects of different drugs or parameters related to the research. Before anaesthesia, a solid fast period of 24-48 h is recommended, but water must be maintained. The nervous and sometimes aggressive behaviour of pigs prevents venous cannulation before anaesthesia, and for this reason preanaesthetics must be administered by intramuscular route in almost all cases, alone or sometimes with anaesthetics such as ketamine. Athough piglets and some swine breeds have thinner skin, adult pigs usually have a wide tissue adipose and their skin is generally hard, and for this reason intramuscular administration is carried out using a large and thick needle (longer than 35-40 mm, over 18-20 G), to ensure that drugs are deposited in muscle. A longer onset and a softer effect of drugs are noted if anaesthetics are administered into adipose tissue. The most used anatomical locations for intramuscular administration are the lateral cervical muscle region (behind the ear), semitendinosus-semimembranosus muscle areas (posterior side of hindlimb), and the lumbar muscle area[8-10].

### *Preanaesthetic protocol*

There are several anaesthetic protocols suitable for pigs, which include the combination of a hypnotic with a sedative and/or an analgesic. This approach provides a degree of anaesthetic suitable for the handling of pigs, although sometimes it is not enough for endotracheal intubation and an inhalation induction by mask is necessary to complete the anaesthetic induction. Oxygen administration *via* face mask is recommended because these combinations induce a variable degree of cardiorespiratory depression. Since the preanaesthetic combination is applied intramuscularly, dissociative agents such as ketamine and tiletamine (in commercial combination with zolazepam) are used[8,10-12]. Alphaxalone has also been evaluated as acting like a hypnotic in swine and when administered intramuscularly together with midazolam provides an excellent sedation, although it is only recommended for small pigs due to the large volume used[13].

Ketamine is the hypnotic habitually used because it can be administered intramuscularly and has a rapid onset, although due to its excitatory effects it must always be combined with a sedative and muscle relaxant[8,10,11]. Alfa-2 agonist sedatives (xylazine, medetomidine, dexmedetomidine) are widely used in both veterinary medicine and biomedicine, providing central sedative effects accompanied with muscle relaxation and analgesia[8,12,14]. Some frequent anaesthetic combinations in transplant researches with pigs are shown in Table 2.

Since the surgical techniques of transplant imply an aggressive approach or major procedures in most cases, at the time of designing an anaesthetic protocol it is important to consider the potential pain of the procedure during the surgery and the post-operative period. Transplantation surgery is major surgery that requires the use of an opioid analgesic in premedication and especially during the surgery, in which constant rate infusions of pure opiods (fentanyl or remifentanil), may be necessary[8,14]. Likewise, a multimodal approach must be used and f NSAIDs must be administered as carprofen[8-10].

### *Anaesthetic induction and tracheal intubation*

Venous catheterization is often performed after the intramuscular premedication and often when tracheal intubation has been accomplished. The auricular veins are the most common access in pigs for the administration of additional intravenous anaesthetic drugs, fluid therapy and for obtaining venous blood samples. However, for transplantation surgery, central venous and arterial catheterizations are recommended (usually external jugular veins and femoral artery), because a major management of electrolyte and acid-base status is required. Moreover, a central venous access allows the monitoring of cardiac output control and pulmonary pressures. This advanced monitoring is especially indicated for research, when pigs must be maintained and controlled under intensive care conditions for several hours or days after surgery[8-10,15].

**Table 2 Intramuscular preanaesthetic combinations for transplantation surgery in pigs**

| Dissociative | Sedative | Analgesic (optional) | Time induction | Duration of anaesthesia |
|---|---|---|---|---|
| Ketamine (5-15 mg/kg), or Tiletamine-zolazepam (5-10 mg/kg) | Medetomidine (5-20 mcg/kg), or Romifidine (60-100 mcg/kg), or Dexmedetomidine (5-20 mcg/kg) | Morphine (0.3-0.5 mg/kg), or Methadone (0.3-0.5 mg/kg) | 5-20 min | 40-60 min |

**Table 3 Intravenous anaesthetic induction in pigs**

| Anaesthetic | Intravenous doses |
|---|---|
| Propofol | 2-5 mg/kg |
| Ketamine | 2-10 mg/kg |
| Tiopenthone | 5-15 mg/kg |

**Table 4 Minimal alveolar concentration of inhaled anaesthetics in pigs**

| Anaesthetic | Minimal alveolar concentration |
|---|---|
| Isoflurane | 1.2-2.0 |
| Sevoflurane | 2.2-3.5 |
| Desflurane | 8.3-10 |

**Table 5 Mechanical ventilation settings for pigs**

| | |
|---|---|
| Tidal volume | 10-15 mL/kg |
| Respiratory rate | 10-15 breaths/min |
| Maximum airway pressure recommendable | 20 cm $H_2O$ |
| Normocapnia (end-tidal $CO_2$ concentration) | 40-45 mmHg |

**Table 6 Recommended doses of constant rate infusion of drugs in pigs**

| Drugs | Bolus intravenous | Constant rate infusion |
|---|---|---|
| Fentanyl | 3-10 μ/kg | 10-30 μg/kg per hour |
| Remifentanyl | 10 μ/kg | 10-50 μg/kg per hour |
| Morphine | 0.1-0.3 mg/kg | 0.1-0.3 mg/kg per hour |
| Dexmedetomidine | 0.5-1 μ/kg | 0.5-1 μg/kg per hour |
| Medetomidine | 1-2 μ/kg | 1-2 μg/kg per hour |
| Ketamine | 0.5-2 mg/kg | 0.1-2 mg/kg per hour |
| Lidocaine | 2 mg/kg | 1-3 mg/kg per hour |
| Midazolam | 0.2-0.4 mg/kg | 0.2-0.4 mg/kg per hour |

Usually it is not possible to perform the intubation after premedication since the metabolization of dissociatives is quick, so the induction of anaesthesia must be completed after the administration of the preanaesthetic combination in order to obtain an adequate relaxation of the laryngopharyngeal structures to perform a tracheal intubation. Propofol (2-5 mg/kg), can be administered intravenously if the ear vein has been catheterized (Table 3). Isofluorane or sevofluorane administration (3%-5%) in oxygen (2-4 L/min) *via* face mask is the most used technique. The use of neuromuscular blocks is initially inadvisable because tracheal intubation is difficult to perform and requires some experience[8-10,15].

Tracheal intubation can be performed in sternal, ventral or lateral recumbency, being a difficult procedure, especially in large pigs because the mouth cannot be opened sufficiently and laryngeal structures are not easily visible. In large pigs a specific straight laryngoscope (15-30 cm length) with a large blade is needed. The diameter of the endotracheal tube oscillates between 7 and 12 mm, depending of the size of the swine. In pigs above 25 kg, the use of a rigid or semi-rigid guide for tracheal tubes avoids bending and facilitates the intubation in sternal recumbency especially. To prevent laryngospasm during tracheal intubation, laryngeal irrigation with local anaesthetic (lidocaine or mepivacaine) is recommended[8-10,15].

### *Anaesthetic equipment*

Pigs can be anaesthetized with human or veterinary anaesthetic machines. A corrugated and reservoir balloon must be selected according to the weight of the pig. Precision vaporizers of isofluorane, sevofluorane or desfluorane can be used attending to minimum alveolar concentration (Table 4), and several fraction of oxyegen can be set up. Mechanical ventilation settings for pigs are similar to other species and are shown in Table 5. For an adequate constant rate infusion of drugs (Table 6), a perfusor or infusion pump must be used.

## PIG AS A MODEL OF TRANSPLANT RESEARCH

Swine is used extensively as a transplant model of different organs, but despite the complexity of these surgical procedures, in many researches of transplantation in pigs, special considerations are not taken into account and normal anaesthetic procedures are performed, but with important limitations.

### *Renal transplantation*

In all the experimental kidney transplantation papers reviewed, even in very recently published papers, a lack in anaesthetic control and monitoring has been found. In most of the pig model studies, anaesthetic protocol is not even mentioned in a number of different

papers[16-19]. Other studies describe the drugs and doses, but no description of the quality of anaesthesia or an evaluation of anaesthesia's influence on patient evolution are mentioned. An intramuscular injectable mixture of a sedative and ketamine[20,21] or tiletamine-zolazepam[22] is the method most described for the induction of anaesthesia in pigs for kidney transplantation. The sedatives used were xylazine[20,22] or diazepam and azaperone[21]. Atropine was also added[20] to the injectable mixture to prevent bradycardia and reduce bronchial secretions. The authors another paper[23] used ketamine IM and thiopental IV directly as anaesthesia inductor agents without the previous use of sedatives. In this case the ketamine dose was increased to 5 mg/kg. Other papers administered propofol as a bolus for the induction of anaesthesia and to achieve an adequate depth of anaesthesia for tracheal intubation, either as a unique drug[22] or combined with fentanyl[21].

Atracurium and cisatracurium are frequently used in human kidney transplantation due to the fact that their duration of action is independent of either liver or kidney function, since other muscle relaxants, such as pancuronium, vecuronium or rocuronium, have a prolonged duration of action in patients with end-stage renal disease[24,25]. This is not a problem in experimental kidney transplantation if the recipient pig is healthy. Few authors describe the use of neuromuscular blockers in pigs. In[21] a bolus of cisatracurium after induction (15 mg/kg IV) was used and pancuronium (0.1 mg/kg IV) was used in[22], an experimental study. Anaesthesia maintenance in pigs is mainly performed using volatile agents, such as halothane 1%-2%[20], isoflurane[22,23] or sevoflurane 2%[21], although some other drugs have been used during anaesthesia maintenance to reduce the volatile agent requirements, such as remifentanil (0.08-0.1 mg/kg per hour)[21]. Among all the reviewed papers, only[22] described that the depth of anaesthesia was assessed by a veterinary anaesthetist throughout the procedure and adjusted accordingly.

Pigs were under controlled ventilation during some experimental kidney transplantations[21-23]. A description was found only when volume-controlled ventilation was applied, such as in[21] (minute volume 8 mL/kg; adapted according to blood gas analysis) or[22] (tidal volume 10-15 mL/kg; a peak inspiratory pressure of 25 cm of water; adjusted to achieve normocapnia, end-tidal carbon dioxide level 35-45 mmHg) studies. Fluids are needed in order to maintain optimum central venous pressure (CVP) and pulmonary arterial pressure. During a review of papers, no description of the type and rate of fluids used was found. Only[22] mentioned the use of Hartmann solution and Gelofusin and the internal jugular vein was used for this purpose.

With regard to perioperative pain control, drugs such as morphine, meperidine or oxycodone should be used with caution in patients with renal failure because these agents or their active metabolites depend on renal excretion and may accumulate[26,27]. Fentanyl, sufentanil, alfentanil and remifentanil are safe for renal function[26,28-30]. Post-operative pain is controlled in different ways in humans, and it has been shown that the choice of intraoperative anaesthetic influences post-operative pain control, since patients receiving propofol had better recovery of psychomotor function and used patient-controlled analgesia more effectively than patients receiving halotane or isoflurane[31]. No proper descriptions regarding perioperative and post-operative pain control have been found in the pig kidney transplantation review.

Hypotension may occur after unclamping the iliac vessels and reperfusion of the graft. Because the renal graft function depends on adequate perfusion, every effort should be made to avoid episodes of marked hypotension. Few studies describe the monitoring performed. CVP was measured using the internal jugular vein[22,23]. The brachial[23] or the auricular artery[22] were cannulated for blood pressure measurement. Oxygen saturation, ECG, temperature and end-tidal carbon dioxide were continuously measured during general anaesthesia[21-23]. In addition, full blood count, glucose, creatinine, urea, sodium, potassium, haemoglobin, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase were measured in one study[21]. Some authors described that the recipient's haemodynamic and metabolic alterations were treated, but no data were published. One paper[23] mentioned that they obtained effecctive anaesthetic maintenance until the experimental end point, and in the[22] study, that the vital signs of all pigs were stable during surgery and the post-operative observation period.

In animal models it has been shown that vessels in the transplanted organ seem to be more sensitive to sympathomimetics, and are thus more likely to compromise renal blood flow to the transplanted kidney, so strong alpha-adrenergic vasoconstrictors, such as phenylephrine, should be drugs used only as a last resort[32,33]. Drugs such as mannitol and dopamine have been used in human kidney transplantation but no references have been found to its use in pigs. Mannitol is usually administered to donors before recovery and to recipients just before unclamping the arterial blood flow, because it may give protection against ischaemic injury and induce osmotic diuresis. The use of a low-dose dopamine (2-3 mcg/kg per minute) to stimulate DA1 dopaminergic receptors in the kidney vasculature to induce vasodilation and increased urine output has been shown to be effective during kidney transplantation[34], whereas other studies have shown no significant improvement[35].

### *Liver transplantation*

Although the initial liver transplantation studies included dogs, pig is the preferred species due to its physiologic and anatomic similarity with humans[36].

Azaperone is a butyrophenone that has been used as a sedative before general anaesthesia for liver transplantation, either as a sole agent at premedication[36,37] or in combination with other drugs, such as ketamine,

diazepam or atropine[21,38,39]. Another pharmacological group used frequently for sedation at premedication in pigs undergoing liver transplantation is that of α2-adrenoceptor agonists, such as xylazine[40-44] or romifidine[45]. Benzodiazepines are also used at premedication for muscle relaxation, generally combined with ketamine and/or a sedative drug since they are minor tranquillizers[21,38,41,46,47]. There are authors that have used parasympatholytic drugs at premedication in pigs undergoing liver transplantation[39,41,43], the main use being as an excessive salivation inhibitor; it is unusual for bradycardia to be a problem in anaesthetized pigs[48].

The most common method is the use of a combination of drugs with different properties to induce a balanced premedication-sedation, such us the administration of sedatives with opioids[49]. Furthermore, the administration of an analgesic before a painful stimulus optimizes the control of pain during the surgery procedure and reduces the dose of analgesic during the post-operative period. In general, mu agonists produce a more profound analgesia and they are recommended for moderate to severe pain and to reduce the necessity of anaesthetics[50]. Several authors have used an opioid at premedication in pigs prior to a liver transplantation[45,51].

Ketamine has been used at premedication in pigs undergoing a liver transplantation by several authors to immobilize the animal and to make easier its manipulation[21,39,40,42,45-47,51,52]. However, ketamine as a sole agent does not induce a surgical anaesthesia, so it would be necessary to combine it with opioids, benzodiazepines and/or sedatives[48]. Another dissociative anaesthetic used in pigs is tiletamine, commercialized with zolacepam, a benzodiazepine[43,44]. Like ketamine, it would be convenient to combine it with other sedative and/or analgesic agents to improve the quality or surgery anaesthesia[48].

For anaesthetic induction in pigs undergoing liver transplantation, several studies have used propofol[21,40,46,53,54], etomidate[39] or barbiturates[36,37,44,47]. These drugs produce a faster onset of anaesthesia with short duration of action after the administration of a bolus. Other authors have used an inhalatory anaesthetic through a face mask for the induction of anaesthesia, after a satisfactory premedication[45,51].

Most of the authors have used inhalatory anaesthetics during the maintenance of anaesthesia in pigs undergoing a liver transplantation. Changes in the depth of anaesthesia are faster than with intravenous anaesthetics, with a faster recovery after the anaesthesia procedure[55]. Isoflurane[36,39,40,42,51,54] and sevoflurane[21,41,44] are the anaesthetics most used. None of these anaesthetics are good analgesics, so many authors used them together with continuous infusion of fentanyl[21,36,40,44,45,56] or remifentanil[54]. Other authors described the use of propofol in total intravenous anaesthesia during the maintenance of anaesthesia in pigs undergoing liver transplantation[52], even combined with a continuous infusion of fentanyl because propofol does not have analgesic properties[46,56,57]. In addition, the pharmacological combinations for maintaining the anaesthetic in pigs during a liver transplantation has been described, with ketamine at 15 mg/kg per hour, fentanyl at 0.02 mg/kg per hour and midazolam at 0.9 mg/kg being used[38].

At induction and during the anaesthetic maintenance in pigs undergoing a liver transplantation it is common practice to the use of neuromuscular blocking agents such as pancuronium[36,39,41,45,51], atracurium[45,51], vecuronium[41] and cisatracurium[21]. These agents are indicated to facilitate orotracheal intubation, and are administered together with hypnotic agents to avoid larynx spasm and to provide the fast control of the airway. Other indications included the prevention of spontaneous movement during the maintenance of anaesthesia, reducing the resistance to ventilation and easing surgical access during the surgical procedure[58].

During a liver transplantation, metabolic (acidosis) and cardiovascular changes (hypotension and bradycardia) are usual. To finish the experiences correctly, it is neccesary to understand these alterations, when they are produced and how to correct them. In human medicine, a liver transplantation procedure can be divided in three phases: (1) dissection phase, includes the lysis of adhesion and the removal of the damaged liver; (2) anhepatic phase, includes the implantation of donor liver; and (3) reperfusion phase, including the anastomoses, haemostasis and closure[59]. The ionized calcium levels can decrease during a liver transplantation, mostly during the dissection and anhepatic phases[60]. The exogenous citrate from blood transfusion could be responsible for this low level of ionized calcium and calcium infusions may be required, such as calcium chloride and calcium gluconate[61]. After reperfusion and with the beginning of the functionality of the transplanted liver, the haemostasis of calcium may be corrected and calcium supplementation may no longer be required.

During the anhepatic phase, the donor liver is implanted. If the surgery technique is infracaval interposition, there is a complete vascular occlusion by clamping the hepatic artery and porta, infrahepatic cava and suprahepatic cava veins. Because the inferior cava venous is blocked, a severe hypotension can develop. These haemodynamic effects depend on the patient, so it is advisable to place a previous temporary test clamp on the inferior vena cava to know the haemodynamic response of the animal before realizing the permanent vascular clamping during the anhepatic phase. Once the liver is positioned, the anastomosis of suprahepatic, infrahepatic and portal veins is completed in that order. The anastomosis of the hepatic artery is carried out before reperfusion or after the restoration of blood flow. During this phase hypocalcaemia and acidosis could be observed, so it is important to monitor these parameters closely. Avoid the aggressive infusion rate of fluids in this phase to maintain blood pressure, because this could result in overload of fluids resulting in cardiopulmonar

compromise and liver and intestinal swelling. At the end of this phase the vascular clamps are removed and each anastomosis is observed for the detection of leaks[59]. The withdrawal of the clamps from the portal vein allows blood flow from splanchnic circulation into the donor liver and is the beginning of the reperfusion phase. The most critical point in this phase is the immediate period after the vascular clamps are removed from the liver graft, mainly seconds or minutes after unclamping the portal vein, as is called as reperfusion syndrome[59]. A decrease in cardiac contractility[62], arrhythmias, bradycardia, severe hypotension and hyperkalemic arrest may be observed. The anaesthetic management must be directed at maintaining or recovering cardiovascular stability. The use of epinephrine, atropine, calcium or sodium bicarbonate could be neccesary[59]. Also, the use of methylene blue has been described as attenuating the haemodynamic changes during reperfusion syndrome[63]. In this phase it is common for an alteration in the metabolism of glucose, and progressive hyperglycaeemia may ensue, due to the glycogenolysis by the donor liver, a decrease in glucose use and insulin resistence. In this phase it is possible that coagulopathy may develop, with resultant bleeding[59].

Severe coagulopathy and intraoperative loss of blood are significant problems in patients undergoing liver transplantation. This alteration in the homeostasis, mainly after receiving the donor liver, is multifactorial and inludes hyperfibrinolysis, depletion of coagulation factors, trombocytopenia and platelet dysfunction. The administration of fresh frozen plasma, red blood cells, platelets and cryoprecipitate are the main therapies for blood loss and coagulopatthy during liver transplantation. However, in humans, the use of these blood products during the liver transplantation has been significantly reduced in recent years due to an improvement in surgical technique, intraoperative management and in patient selection[59]. Currently, the administration of haemostatic agents, such as aminocaproic acid, tranexamic acid, *etc.*, are being evaluated as adjunctive therapies[64-69]. It is important to restore diuresis during the procedure to facilitate fluid management and to protect the kidneys during the renal ischaemia in the anhepatic phase. Drugs used to maintain the urine output are loop diuretics, dopamine and mannitol[59].

Most of the pigs used in experimental procedures are euthanized at the end of the surgical procedure. However, some authors keep them alive to continue with the investigation. Authors of[41] described the use of buprenorphine during the post-operative period. Authors of[36] described this period in detail, evaluating the ingestion of the animals and the follow-up treatment with immunosuppression, antibiotics and buprenorphine as analgesic.

### *Heart transplantation*

Porcine models have been used to study cardiovascular disease and transplantation, but have been associated with problems, such as friability of certain organs, anaesthesia difficulties, ventricular fibrillation and oedema[70]. Cardiopulmonary bypass (CPB) models have been described only for two to four hours[71-73] or using swine models not of mature age or body weight, which cannot be considered as true adult size[74] and do not have the same responses to stress as do larger or mature swine[71].

Authors of one paper[75] described a swine model for long-term CPB using an adult pig weighing more than 80 kg. The anaesthesia protocol used for this model was very simple since ketamine and atropine sulphate were given intramuscularly followed by sodium pentobarbital intravenously to maintain a proper level of anaesthesia. Anaesthesia was maintained throughout the entire procedure using sodium pentobarbital in the mechanically ventilated pig. It maintained normothermic CPB and did not develop any previously described problems. Priming the CPB circuit with a combination of more adult blood than crystalloid solution possibly prevented the tissue oedema often seen in such procedures. HR, arterial pressures, urine production, hematocrit, electrolytes, glucose and lactate were within normal range throughout the CPB procedure and were not different from each other from the beginning to the end of CPB. Only the activated clotting time was maintained artificially higher than 1000 s. Prior to the initiation of CPB and throughout the entire procedure and $pO_2$ was also kept high. Modifications to the procedure, including a higher blood-to-crystalloid ratio in the priming solution, a slightly higher oxygen concentration in the circuit and maintaining the acid base status seemed to contribute to the success of this model.

Recently, the use of porcine cardiac xenografts has become more feasible because of the production of transgenic pig organs expressing human complement regulatory proteins on the endothelium, and continued surgical experimentation involving baboons will contribute to the understanding of the immunological basis for xenograft rejection. Orthotopic pig-to-baboon xenogeneic heart transplantation is the only accepted preclinical animal model for cardiac xenotransplantation[7]. Anaesthetic management of the orthotopic pig-to-baboon model is complicated by ischaemia-reperfusion injury, the use of CPB and the additional immunological processes of xenogeneic transplantation.

A variety of animal experiments[76,77] and human studies[78-80] have investigated the benefits of different anaesthetic regimens in cardiac surgery, suggesting a protective effect of halogenated volatile anaesthetics on the myocardium by mimicking ischaemic preconditioning.

Santerre *et al*[81] described in detail a balanced anaesthetic technique for use in baboons undergoing abdominal porcine cardiac xenografting, and discussed intraoperative monitoring and treatment of the haemodynamic consequences related to infrarenal, aortic cross-clamping. The pharmacological techniques employed were found to be safe and reliable.

### *Others types of transplant*

Swine has been used in other models of transplant such as pancreas[82], cornea[83], duodenum[84], uterus[85], vascularized composite allotransplantation[86], ureter-bladder[87] and lung[88], although in general the anaesthetic considerations are similar to most common transplant in pigs.

## CONCLUSION

Swine is a common research model and a complete knowledge of the different protocols of anaesthesia and their perioperative care is important to develop transplant researches without complications. Pigs are excellent models of research and allow a more direct translation of results than laboratory animals, so they will continue to be frequently used in transplant research models.

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**P- Reviewer**: Mentes O, Wong KL
**S- Editor**: Tian YL **L- Editor**: A **E- Editor**: Jiao XK

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DOI: 10.5313/wja.v4.i3.83

*World J Anesthesiol* 2015 November 27; 4(3): 83-90
ISSN 2218-6182 (online)


MINIREVIEWS

# Update in perioperative anesthetic management of pheochromocytoma

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Author contributions: All authors had participated drafting the article and making critical revisions related to important intellectual content of the manuscript, and final approval of the version of the article to be published.

Conflict-of-interest statement: None of the authors have any commercial, personal, political, intellectual, or religious interests.



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Received: April 27, 2015
Peer-review started: May 7, 2015
First decision: June 4, 2015
Revised: August 23, 2015
Accepted: September 25, 2015
Article in press: September 28, 2015
Published online: November 27, 2015

## Abstract

Pheochromocytoma is a tumor that originates from either chromaffincells in adrenal medulla or in other paraganglia tissues of the sympathetic nervous system. The perioperative management is quite challenging especially in view of hemodynamic fluctuations. Pheochromocytoma is challenging in view of the impact of excessive and depleted catecholamines in the perioperative period. It requires a through preoperative evaluation and optimization with meticulous intraoperative management. The postoperative period requires vigilance to prevent any untoward complication. In this review we review these concepts based on recent evidence for an optimal outcome.

**Key words:** Phaeochromocytoma; Anaesthesia; Surgery; Analgesia; Drugs



**Core tip:** The paper is a comprehensive review of the most important pathophysiological and diagnostic issues, preoperative optimization, and anesthesia management of pheochromocytoma. It describes advanced imaging and biochemical techniques for diagnosis and localisation. Once considered nightmare by anaesthesiologist, pheochromocytoma have improved outcome nowadays due to widely available vasoactive drugs, monitors and perioperative care. Also, availability of laparoscopic and robotic adrenal-sparing adrenalectomy has reduced hospital stay and hastened recovery.

Gupta A, Garg R, Gupta N. Update in perioperative anesthetic management of pheochromocytoma. *World J Anesthesiol* 2015; 4(3): 83-90 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/83.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.83

## INTRODUCTION

Pheochromocytoma is a tumor that originates from

either chromaffin cells in adrenal medulla or in other paraganglia tissues of the sympathetic nervous system. Adrenal is the origin for majority of tumor accounting 80% and rest are from extra adrenal site[1]. Majority of them are benign and may be associated with familial syndromes like multiple endocrine neoplasia (MEN) syndromes, von Recklinghausen disease or von Hippel-Lindau (VHL) syndrome in 10% of the patients. In a few patients pheochromocytoma have been found arising from atypical sites like head and neck, pericardium, inferior mesenteric artery (the organ of Zuckerkandl), aortic bifurcation, other chromaffin tissue in the abdomen, pelvis, and thorax[2,3].

## GENETIC MUTATIONS AND PHEOCHROMOCYTOMA

The formerly used rule of 10 for pheochromocytoma (10% of tumors are malignant, bilateral and extra adrenal) is not convincing with present evidence[4]. Pheochromocytoma may occur sporadically in majority of cases but as high as 40% children and 25% adults may have an associated gene mutation[5,6]. Hereditary pheochromocytoma may be associated with MEN type 2 with RET proto-oncogene mutation, VHL syndrome with *VHL* gene mutations, von Recklinghausen disease with *NF1* gene mutation and succinate dehydrogenase subunit D genes mutation in familial non-syndromic pheochromocytoma[5-7]. Despite multiple gene mutations have been associated with pheochromocytoma, the testing for gene mutations in all the cases is not considered appropriate and is not cost effective.

## CLINICAL PRESENTATION

The presenting signs and symptoms are primarily due to release of catecholamine or their metabolites in the body[1,8-12]. Most of the pheochromocytoma sites except head and neck tumors (less than 5%) produce, store, metabolize and secrete catecholamines or their metabolites[8]. The usual symptoms include hypertension, palpitations, headache, sweating, fatigue, nausea, weight loss, constipation, flushing, fever and pallor. The prolonged exposure of increased concentrations of catecholamines may result in dilated cardiomyopathy, ventricular failure, myocardial infarction, arrhythmia, stroke or other vascular ischemic symptoms. The classical triad of headache, sweating and palpitations may be seen in up to 40% of patients[9,10]. Headache and hypertension occur in predominantly norepinephrine secreting tumors whereas other symptoms like palpitations, sweating, anxiety, panic etc suggest epinephrine or dopamine secretion[11]. Stimulation of sympathetic nervous system may release neither excessive quantities of norepinephrine into the synaptic cleft. Due to proximity of norepinephrine to its receptors, the response is exaggerated even with small increments and patient may present hypertensive crises.

In addition a number of metabolic derangements like diabetes (decreased insulin and increased hepatic glucose output), lactic acidosis, hypercalcemia (parathyroid adenomas), diarrhea and fluid and electrolyte imbalance (vasoactive intestinal peptide secreting tumors) may also be seen in some patients with pheochromocytoma[10-12]. Some patients may be asymptomatic due to receptor down regulation. In such patients, the sympathetic reflexes may be blunted, leading to severe hypotension and shock during unrelated surgery. The symptoms of pheochromocytoma may also be mimicked by many endocrine (hyperthyroidism, menopausal syndrome, carcinoid), cardiovascular (heart failure, arrhythmias), ischemic heart disease and neurological (migraine, stroke) diseases. So, we need to confirm the diagnosis with further testing[12].

## DISCUSSION

Once the signs and symptoms are suggestive of pheochromocytoma, the diagnosis can be confirmed by plasma epinephrine, norepinephrine and urinary catecholamine metabolite [vanillyll mandelic acid (VMA)][1,8,11,13-15]. But since the catecholamines may be released sporadically, these tests have low sensitivity and low specificity. The excessive production of catecholamines is metabolized in the tumor by catechol-o-methyl transferase to metanephrins which can be measured in the plasma[8]. They have a sensitivity of 99% (negative tests rule out pheochromocytoma) and should be carried out as the first test in patients with clinical symptoms and normal catecholamines[11,13]. Also high plasma metanephrin to epinephrine and normetanephrine to norepinephrine ratios are suggestive of pheochromocytoma. The 24 h urinary metanephrins has been found to have high sensitivity (97%) for pheochromocytoma. The product of normalised metanephrin and normetanephrine (100% sensitive and 99% specific) and serum chromogranin A have also been used for diagnostic purpose[14,15].

The other tests reported include clonidine suppression test glucagon stimulation test and selective adrenal vein sampling (not done now days)[13-15]. In clonidine suppression test, plasma epinephrine and norepinephrine are measured before and 3 h after 0.3 mg clonidine. In pheochromocytoma there will be less than fifty percent reduction in epinephrine and norepinephrine and less than 40% reduction plasma metanephrin values[14].

## LOCALIZATION

Once the diagnosis is confirmed by history and biochemical testing, we need to localize the tumor to decide the treatment plan[1,8,9,16]. Surgical resection is the only curative procedure for these tumors. Both magnetic resonance imaging (MRI) and computerized tomography (CT) provide accurate and consistent anatomical identification of adrenal tumors as small as

1 cm in the majority of cases[16]. Contrast enhanced CT further increases its sensitivity but MRI is slightly better than CT. Gadolinium enhanced MRI can be used in children, pregnancy and patients with contrast allergy. In extra adrenal, metastatic and recurrent tumors, the sensitivity of both MRI and CT decreases (< 90%)[9,16]. Such cases need to be identified with radio nucleotide [meta-iodobenzyl guanidine (MIBG)] testing. MIBG has specificity as high as 100% but it may be taken up by neuroblastomas, medullary carcinoma thyroid, carcinoid and small cell carcinomas of lung. Also certain drugs like labetolol, reserprine, calcium channel blockers and some tricyclic antidepressants may interfere with uptake of MIBG and give false negative tests.

The positron emission tomography scan are nowadays available and become important in cases where conventional imaging is unable to detect the tumor in patients with positive biochemical testing[16].

## PREOPERATIVE PHARMACOLOGICAL CONTROL

The control of symptoms due to excessive release of catecholamines are essential as preoperative pharmacological preparation reduces the mortality to less than 3%[9,10,13,16-23]. The surgery is rarely an emergency and anesthesiologist has time to optimize to control blood pressure, heart rate and arrhythmias. The advantages of preparation are: (1) Decreased vasoconstriction and restoration of vascular volume; (2) Normalization of hematocrit; (3) Symptom control; (4) Reversal of myocardial ischemia; and (5) Reduced intraoperative hemodynamic fluctuations.

### *Pharmacological agents*

Various drugs have been used to achieve the optimal status prior to surgical intervention[16-23]. These include:

**Alpha blockers**: Phenoxybenzamine is a non-selective α blocker and is considered the main stay of perioperative control. It has a long duration of action and allows twice daily ingestion[16]. It can be administered orally (10 mg twice a day upto 1 mg/kg per day) or intravenous (0.5 mg/kg per day over 5 h for 3 d). It takes 2-3 wk for treatment to be effective. It produces a non-competetive blockade of the receptor that prevents the effects of surges of catecholamines during preoperative period. This also blocks the α2 adrenoreceptor and prevents feedback inhibition exercised by presynaptic adrenergic neurons leading to uninhibited release of norepinephrine at the cardiac sympathetic nerve endings and consequent undesirable chronotropic and inotropic side effects. Also, it is a non competitive blocker and has a long duration of action. Beta-blockers are given to control tachycardia. It may also lead to side effects due to central α2 blockade like somnolence, peripheral edema, headache, stuffy nose, *etc*.

**Selective α1 blockers:** Doxazosin, prazosin and tetrazosin are also used for optimization and lack reflex tachycardia[16,17]. They may produce profound hypotension due to uninhibited norepinephrine reuptake and its inhibition at postsynaptic α1 receptors. They are usually administered at bedtime with adequate hydration. Doxazosin is administered as a single dose (1-16 mg); prazosin and tetrazosin are administered 4-6/h. A preoperative blockade of 2-3 wk is required to optimize myocardial function.

**Beta blockers**: β blockers given in perioperative period limit the signs and symptoms due to increased circulating catecholamines (supraventricular and ventricular arrhythmias) and control tachycardia due to α blockade[16]. If a β blocker is started before effective α receptor blockade, the vasoconstrictor effects of α receptor go unopposed may produce dangerous hypertension[19]. Cardio selective agents like atenolol (25-50 mg) and metoprolol (50 mg) are preferred drugs. Labetalol β blockade capability is more than α blockade capability (1:7) and it also interferes with imaging by preventing uptake of $^{131}$I MIBG.

**Calcium channel blockers:** (Amlodipine 10-20 mg/d, nicardipine 30-90 mg/d or verapamil 180-240 mg/d) inhibit NE-induced intracellular calcium influx and prevent catecholamine-induced coronary spasm, myocarditis, and attenuate hypertensive responses to noxious stimuli. They do not produce hypotension and are preferred in normotensive patients with occasional episodes of paroxysmal hypertension[16]. Clevidipine butyrate is an intravenous an ultrashort-acting, third-generation dihydropyridine calcium channel blocker that inhibits calcium influx in arterial smooth muscle, causes arterial vasodilation and decreases in peripheral vascular resistance. It is a novel agent for hemodynamic control in the management of pheochromocytoma before a tumor resection[20]. Clevidipine has a fast onset (1-2 min), is rapidly titratable, has a fast offset (5-15 min), and has proven safety and efficacy for acute perioperative hypertension. Since its preparation contains soybean oil and egg yolk phospholipids, it is contraindicated in patients with soybean, soy product, egg, or egg product allergies and in patients with lipid metabolism deficiencies[20].

**Alpha-methylpara tyrosine:** Methyl-para-tyrosine (MPT) is a competitive inhibitor of tyrosine hydroxylase (rate-limiting step in catecholamine biosynthesis)[16,18]. This reduces catecholamine stores and their release on stimulation of the tumor. In MPT is especially useful in extensive metastatic disease to control refractory blood pressure or in patients in which conventional drugs are not tolerated due to side effects (heart failure: β blocker and tachycardia: α blocker). Its use in combination with α blocker has shown to result in a better blood pressure control and less need for use of antihypertensive

medication or pressors during surgery. However, its usefulness is limited due to associated side effects like diarrhea, crystalluria, depression, galactorrhea, anxiety and extra pyramidal symptoms.

**Magnesium sulfate**: It inhibits the release of catecholamine, directly inhibits catecholamine receptors, and is a calcium antagonist. It attenuates catecholamine release due to noxious stimuli (*e.g.*, endotracheal intubation) and abolishes the arrhythmias induced by epinephrine. It also profoundly dilates the arterioles, reduces the peripheral vascular resistance (after load), and exerts minimal effect on venous return (preload)[16,22]. The beneficial effects are more pronounced during the peri-operative period and thus, can be considered an attractive option for catecholamine blockade in patients undergoing tumor resection[22]. It has been found effective for resection of pheochromocytoma in children, during pregnancy and patients presenting with arrhythmias[23]. Its use is associated with sedation, prolonged neuromuscular blockade and muscle weakness.

**$\alpha$2-agonists**: Clonidine is a well-known presynaptic $\alpha$2-adrenoreceptors agonist. It reduces sympathetic tone reduces blood pressure and anesthetic requirements[16]. Dexmedetomidine is a selective $\alpha$2-adrenoceptor agonist and has sedative and analgesic properties. The decreased BP and heart rate are attributed to the decreased catecholamine levels. It can blunt sympatho-adrenal responses to tracheal intubation and surgical stimuli[21].

## PREOPERATIVE MANAGEMENT

The objectives of preoperative evaluation are to ensure adequate $\alpha$ blockade, assess myocardial function, minimize organ complications, ensure normovolemia and correct hyperglycemia and electrolyte abnormalities. Adequacy of blockade is assessed using Roizen's criteria[24]: (1) BP < 160/80 mmHg; (2) Orthostatic hypotension not less than 80/60 mmHg; (3) No more than 1 ventricular premature contractions (VPC) in 5 min; and (4) No new ST-T changes on the ECG over the last week.

The achievement of these parameters suggests an optimization of the patient with regards to effect of catecholamine. Also, the cardiovascular evaluation needs to be done and includes a baseline ECG for evaluation of any myocardial ischemic changes, left ventricular hypertrophy and/or strain. An echocardiogram may further detect ventricular dysfunction, evaluate improvement with therapy and diagnose dilated cardiomyopathy.

## ANESTHETIC MANAGEMENT[25-29]

The anesthetic management and monitoring during surgery will depend upon the extent of surgical approach. Traditionally the surgery is performed in open lateral retroperitoneal approach but sometimes transabdominal approach may be required. Recently laproscopic transperitoneal resection of the tumor is being done. Anesthetic plan will depend upon the surgical approach and patient positioning. Good communication between anesthesiologist and surgeon is important during the perioperative period[25].

### *Premedication*

Preoperative sedation and good communication by the anesthesiologist help in decreasing anxiety and prevent marked hemodynamic fluctuations in the immediate perioperative period. Oral benzodiazepines and H2 receptor antagonist can be given. Short acting selective $\alpha$-1 adrenergic blockers should be administered in the morning of surgery but longer acting drugs (Phenoxybenzamine/doxazosin) should be stopped 12-24 h prior to schedule surgery[25] (Table 1).

### *Operating room preparation*

The infusions of hypotensive drugs [sodium nitroprusside (SNP) 0.01%, nitroglycerine (NTG) 0.1%, esmolol 1 mg/mL and norepinephrine 40 mcg/mL] and vasoactive drugs (magnesium sulfate, labetalol, diltiazem, nicardipine and lidocaine 2%) needs to be prepared in the operating room. Fluids in form of colloids, crystalloids, blood and blood products should be readily available (Table 2).

### *Anesthesia induction and maintenance*

Two large bore (14G) peripheral intravenous access should be secured. The pain and anxiety associated with these procedures can lead to sudden hypertensive response. Invasive lines like radial artery and central venous cannulation should be secured under local anesthetic infiltration supplemented with intravenous midazolam. The monitoring includes continuous electrocardiogram, pulse oximeter, capnograph, temperature and urine output. The invasive monitoring includes central venous pressure and invasive arterial blood pressure monitoring.

Anesthesia induction and tracheal intubation must be smooth and hemodynamic response to intubation should be avoided. Various drugs/techniques have been used to blunt sympathetic response such as nitroprusside, nitroglycerin, magnesium sulfate, urapidil, opioids (fentanyl, remifentanyl), esmolol, nicardipine, and lidocaine have been described.

### *Induction of anesthesia*

Almost all induction agents have been used safely and the choice of drugs depends upon institutional and individual practice. Both thiopentone and propofol are the commonly used drugs during induction of anesthesia. Propofol is preferred because it produces vasodilatation and blunts to the hypertensive response to laryngoscopy and intubation[26]. Etomidate is also recommended due to its cardiovascular stability[27,28]. The use of all the drugs that increase sympathetic tone

**Table 1 Drugs commonly used in preoperative preparation of pheochromocytoma**

| Drug name | Dosages | Additional information |
|---|---|---|
| Phenoxybenzamine | 60-50 mg | Dizziness, headache, nasal stuffiness peripheral edema and prolonged hypotension (long postoperative blockade) |
| Doxazosin | 2-6 mg | Short acting, no prolonged hypotension |
| Beta blockers | | |
| Propranolol | 80-120 mg | Careful in patients with asthma, conduction disturbances, severe heart failure. May cause severe bradycardia and postural hypotension |
| Metoprolol | 50-100 mg | |
| Labetalol | 5-10 mg q5 min | |
| Calcium channel blockers | | |
| Verapamil | 120-240 mg | Careful in patients with n AV blocks, hypovolemia, sinus sick syndrome, and heart failure |
| Diltiazem | 180 mg | |
| Nifedipine | 30-90 mg | Side effects: Elevated liver enzymes, headache, constipation, dizziness, fatigue, edema |
| Clonidine | 0.1-1.2 mg | |
| Dexmedetomidine | 1 mg/kg in 10 min, 0.7 mg/kg per hour infusion | Dizziness, rebound hypertension side effects: depression, anxiety, dry mouth, bradycardia |
| Magnesium sulfate | 1-8 mg loading dose, 1-4 mg/h maint | Potentiates neuromuscular blockade, caution in heart block and renal failure |
| Urapidil | 10-15 mg/h | Caution because of severe hypotension |
| Alpha methyl-p-tyrosine | 1-4 g/d | Crystaluria, extra-pyramidal and psychic disturbances |

**Table 2 Commonly used drugs during resection of pheochromocytoma**

| Drug | Dosages | Additional information |
|---|---|---|
| Fenoldopam | 0.2 mg/kg per minute | Tachycardia, hypokalemia<br>Cautions in patients with CVA |
| Sodium nitroprusside | 1-2 mg/kg per minute | Cyanide toxicity, reflex tachycardia, severe hypotension |
| Nitroglycerine | 25-250 mg/min | Reflex tachycardia, tachyphylaxis<br>Methemoglobinemia, cerebral vazodilation |
| Nicardipine | 5.0 mg/h | Hypotension, bradycardia, heart failure, WPW syndrome |
| Phentolamine | 1-5 mg | Minimum side effects |
| Beta blockers | | Careful in patients with asthma, conduction disturbances, severe heart failure. May cause severe bradycardia and postural hypotension. May potentiate effect of other drugs (like CCB) |
| Esmolol | 5-10 mg × 3 min | |
| Metoprolol | 2.5-5 mg × 2 min | |
| Labetalol | 5-10 mg | |
| Epinephrine | 1-20 mg/min | A and β agonist, positive inotropic, chronotropic effect and increases BP |
| Norepinephrine | 1-30 mg/min | α/β1 agonist, decreases organ blood flow |
| Dopamine | 5-20 mg/kg per minute | α/β/dopamine dose dependent agonist, may cause tachycardia and dysrthymias |
| Vasopressin | 0.1-0.4 units/min | May cause MI |

or may precipitate hypertensive crisis, such as ketamine, ephedrine, pancuronium and metoclopramide must be avoided[27,28]. Droperidol may cause hypertensive crisis and should be avoided[29].

### *Inhalation agents*

Sevoflurane is preferred because it is cardio-stability and lack of arrhythmogenic potential[30]. Isoflurane lowers peripheral vascular resistance and blood pressure and can be used[31]. Halothane (arrhythmia potential) and desflurane (sympathetic stimulation) are not preferred in pheochromocytoma[32].

### *Muscle relaxants*

During induction, use of succinylcholine can be hazardous as it may stimulate the autonomic ganglia (cause arrhythmia) and fasciculations due to succinylcholine may squeeze the gland and precipitate hypertensive crisis[33]. Atracurium and tubocurarine release histamine and should be avoided[34]. The recommended drugs are vecuronium, rocuronium and cisatracurium[27,28].

### *Total intravenous anaesthesia*

Propofol and remifenatnyl are hemodynamically safe and decrease heart rate (central vagal nuclei stimulation). Remifentanil is an ultrashort acting opioid and acts by binding to μ-receptors in brain, spinal cord, and peripheral neurons[35]. Propofol is also a short acting drug which acts by increasing inhibitory γ-aminobutyric (GABA) synapses and inhibiting glutamate. Both the drugs together decrease the hemodynamic response during pheochromocytoma resection. The pharmacological profile of these drugs makes total intravenous anesthesia a safe anesthetic choice for such patients[36]. Recently, dexmedetomidine has also being used to provide a satisfactory preoperative sedation and intraoperative hemodynamic control. It also reduces anesthetic requirements and improves postoperative analgesia. Dexmedetomidine has been described recently for pheochromocytoma resection in an adult[27].

### *Intra operative hypertensive crises*

During the intraoperative period, hypertension can occur

during induction, insertion of central lines, intubation, surgical incision, creation of pneumoperitoneum and tumor manipulation[37]. Risk factors for intraoperative hemodynamic instability include large tumor, baseline mean arterial pressure more than 100 mmHg and a high plasma norepinephrine concentration. Hemodynamic crisis may be due to epinephrine or norepinephrine release. Epinephrine induced crisis will present with tachyarrhythmia (paroxysmal supraventricular tachycardia, VPCs and ventricular arrhythmias) with increased systolic blood pressure and diastolic blood pressure (> 100 mmHg)[26,27,37]. Drugs like esmolol (0.5-1 mg/kg intravenous bolus or infusion), labetalol 5-10 mg intravenous, adenosine or intermittent boluses of metoprolol (1-2 mg intravenous) will help in controlling the crises. Amiodarone or lidocaine may be required in patients with poor left ventricular function. Norepinephrine crises are more common and characterized by severe bradycardia with profound hypertension. Rapid intravenous infusion of SNP through the central vein is usually effective, but esmolol needs to be added to control resultant tachycardia. The hypertension can also be controlled by deepening the anaesthesia or use of drugs like nicardipine, NTG, magnesium, *etc*. A combination of nicardipine (titrable short-acting calcium channel blocker) and esmolol (titrable ultrashort acting selective β1-receptor antagonist) can be used as an alternative especially in asthmatic patients[26,27]. Fenoldopam (dopamine1 receptors agonist) is a suitable titrable drug (dose of 0.2 mg/kg per minute) and causes peripheral vasodilatation and reduces blood pressure[37].

After the adrenal gland has been removed, severe hypotension may be result due to blood volume depletion (because of diuretics), residual action of vasodilators, bleeding, catecholamine withdrawal, adrenoceptor down regulation and steroid withdrawal (bilateral adrenalectomies)[26,27]. Initial treatment should be volume replacement upto 2-4 L to restore CVP to 10-12 mmHg. If ineffectivewe may require combination of multiple inotropes like epinephrine, norepinephrine, neosynephrine (pure α-adrenergic agonist), ephedrine, dopamine and vasopressin.

## ANALGESIA

Epidural analgesia and spinal anesthesia have been used in patients planned for open procedures with large incisions[26,27]. However, a combination of central neuraxial block with general anaesthesia must be balanced against the risk of hypertension during its placement and possibility of post-excision hypotension[38,39]. Drugs like morphine (histamine release) and pethidine (sympathetic stimulation) are not preferred in pheochromocytoma. Fentanyl is a potent opioid and can be used as bolus (3-5 μg/kg) or infusion (1-2 μg/kg per hour)[27]. Non-steroidal anti-inflammatory drugs provide analgesia in patients with laparoscopic and robotic-assisted adrenalectomy.

Now days, laparoscopic arenalectomy and more recently, robotic-assisted adrenalectomy is being done[40-42]. These may be associated with reduced blood loss and vasodilator use, due to decreased/delicate tissue handling. It also produces less postoperative pain, decreases hospital stay and recovery period. Laparoscopic approach may not be feasible in cases of invasive carcinoma also. Carbon dioxide pneumoperitoneum can induce catecholamine release by a pheochromocytoma, leading to increase mean arterial pressure and central venous pressure[43,44].

## POSTOPERATIVE MANAGEMENT

Approximately half of patients remain hypertensive for a few days due to elevated catecholamine stores in adrenergic nerve endings, which tend to persist for 1 wk after resection[26,27]. Persistent hypertension may indicate fluid excess, return of autonomic reflexes, inadvertent ligation of a renal artery, or presence of residual tumor.

Some patients may have persistent hypotension due to blood loss, altered vascular compliance, and residual preoperative adrenergic blockade. Postoperative blood glucose monitoring should be done because hypoglycaemia has been reported. Patient operated for arenalectomy may have postoperative drowsiness/unconsciousness and may be related to hypoglycemia, depletion of CNS catecholamine and multiple episodes of hypertensive crises intraoperatively may lead to cerebrovascular accident[44].

To conclude, pheochromocytoma is a challenging in view of the impact of excessive and depleted catecholamines in the perioperative period. It requires although preoperative evaluation and optimization with meticulous intraoperative management. The postoperative period requires vigilance to prevent any untoward complication.

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**P- Reviewer**: Fassoulaki A, Feltracco P, Ozcengiz D
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