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## Update in Anaesthesia



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# Editor's Notes

**The editorial team of Update in Anaesthesia hopes you have all had a good start to 2020, and that it proves to be a year filled with safe anaesthesia, and satisfactory personal achievement.**

In this edition we have research articles, reviews, case reports and letters, from colleagues all over the world on a variety of anaesthesia topics. We have also reprinted (with permission) an article from the South African Medical Journal, as well as 5 ATOTWs (Anaesthesia Tutorials of the Week), which are relevant to anaesthesia practice everywhere. Whether you practice in the most sophisticated first world scenario, or a poorly equipped rural district hospital in a low middle income country, we trust that you will enjoy reading UIA volume 35, and that you will find something of relevance to your practice.

Looking ahead, the World Congress of Anaesthesiologists will be held in Prague in the Czech Republic from 5th-9th September 2020. These quadrennial congresses organised by the WFSA are an amazing opportunity to meet fellow anaesthesiologists from around the world, as well as being of great scientific and educational value. No matter what your area of interest is in Anaesthesia, there really is something for everyone with many excellent speakers and interesting workshops. Registration for the Congress is now open and we look forward to seeing you there. www.wcaprague2020.com

As you will have read in the last edition of Update in Anaesthesia, Dr Victoria Howell and I have taken over as Editors-in-Chief. However, despite the change of leadership, the aims and objectives of Update in Anaesthesia remain the same; that is to produce high-quality, clinically relevant educational articles that can be used by anaesthesia practitioners the world over. We aim to produce one themed edition a year and an edition with a variety of anaesthesia topics as we have in this edition. We welcome your contributions to the journal, and if you have any suggestions about the journal or manuscripts that you would like to be published, please do not hesitate to get in touch. You can find contributor guidelines and submit manuscripts directly through our online submission system at:

**www.wfsahq.org/uia-authors-page**

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Research

# Implementation of the WHO surgical safety checklist in a West African teaching hospital: a quality improvement initiative

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## Abstract

**Background:** This study aimed to evaluate the implementation of a surgical safety checklist (SSCL) at an academic hospital in Ghana.

**Methods:** The WHO SSCL was locally adapted and introduced in all surgical cases at Cape Coast Teaching Hospital (CCTH), Ghana. A chart audit of 2.5% of surgical cases over 12 months was conducted. The main outcome measures included: 1. Percentage of cases where the SSCL was present, 2. Percentage complete, 3. Where the SSCL was incomplete, percentage complete at each critical point (before induction of anesthesia, before skin incision, and before leaving the operating theater), 4.Information missing in incomplete charts.

**Results:** One hundred surgical cases were evaluated. The SSCL was present in 93% (95% CI 88%-98%) of cases reviewed, but complete in only 21% (95% CI 10.5%- 29.0%) of all cases, and 3.6% (95% CI -3.3%-13.0%) of C-sections. The last part of the checklist was most likely to be completed. The most common missing information was patient demographics.

**Conclusion:** The SSCL was introduced at CCTH over 1.5 years. While uptake was high, the majority of cases were incomplete. This QI activity informed a revision of the SSCL and a strategy for periodic evaluation to facilitate its sustainable use.

**Key Words:** patient safety, quality improvement, anaesthesia

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## INTRODUCTION

Kybele Inc. is a non-profit organization based in North America dedicated to improving maternal care worldwide. Kybele has demonstrated improvements in maternal and neonatal care in low middle-income countries by implementing successful changes in the local environments.[1] It has had a prominent presence in Ghana since 2004.

Cape Coast Teaching Hospital (CCTH) is located in Cape Coast, Central Region, in Ghana. In 2015, it completed its transition from a community to a teaching hospital. That year, there were 2854 births. Maternal mortality ratio (MMR) was 1,111 per 100,000 live births, an increase from 772 per 100,000 live births in 2014.[2] By comparison, the country-wide MMR in 2015 was 319.[2] The primary causes of maternal deaths were hypertensive disorders of pregnancy, hemorrhage and sepsis, accounting for over 90% of MMR. There were 984 caesarean deliveries representing 33% of total surgeries at CCTH. Institutional surgical deaths were defined (at CCTH) as deaths in the operating theatre or recovery room. There were eight in 2015.[2]

The local hospital management identified a need to improve maternal care and pursued a collaboration with Kybele Inc. This collaboration was designed to address maternal and newborn health, anesthesiology and critical care needs at CCTH. The program was an expansion of an existing collaboration between Kybele, Inc. and the Ghana Health Service (GHS) which began in January 2007.[1] The two cooperated in the development of a quality improvement initiative at CCTH which resulted in the Maternal and Newborn Quality Improvement Action Group (MNQIAG). The ultimate objective of this group is to reduce maternal and newborn morbidity and mortality through an innovative, systematic quality

improvement approach designed to build local organizational capacity and health facility systems. The purpose of the MNQIAG is to coordinate quality improvement initiatives related to Maternal Newborn care at CCTH. One such strategy was the introduction of the surgical safety checklist in caesarean deliveries.

The World Health Organization set out the "Safe Surgery Saves Lives" programme in 2008 detailing a number of goals to improve surgical safety.[4] As part of this programme, WHO encouraged the use of a surgical safety checklist (SSCL) in a model that is simple, widely applicable and measurable. The SSCL is a cost-effective tool that aims to enhance patient safety by improving communication in the operating room. Use of the SSCL has been shown to reduce surgical morbidity by one third and surgical mortality by half.[5] Despite this evidence, there are still places in the world where it has not been introduced. CCTH is a center where the checklist had not been implemented.

Based on previous evidence[5], the WHO Surgical Safety Checklist was proposed as a process to improve the delivery of care while reducing inefficiencies within the CCTH operating theaters. Initially its introduction was planned for caesarean deliveries only due to the focus of the collaboration with Kybele on improving obstetrical care. Based on feedback from the Departments of Anesthesia and Obstetrics and Gynecology, the project evolved to include all surgical cases. The current quality improvement initiative was developed in order to evaluate the process of implementation of the SSCL at CCTH and to develop strategies for improved uptake and completion of the SSCL. The current report adheres to the SQUIRE 2.0 (Standards for Quality Improvement Reporting Excellence) guidelines.[6]

## Materials and Methods

*Context:* This was a quality improvement activity intended to introduce the surgical safety checklist to Cape Coast Teaching Hospital and to evaluate its implementation over time to completion. A multidisciplinary team consisting of an obstetrician/gynaecologist (MM), certified registered anaesthetist (HT) and an operating room nurse (EMQ) at CCTH led the CCTH/Kybele adaptation of the checklist[4] to suit the specific context of CCTH. For the remainder of the manuscript, "SSCL" will be used to refer to the version of the surgical safety checklist that was implemented at CCTH.

The resulting checklist was piloted in three elective caesarean deliveries of varying levels of complexity and one pediatric general surgery case. This took place in February 2016 during one of the two annual visits from the Kybele team. The SSCL team demonstrated its use before induction of anesthesia (the circulating nurse confirms the patient's identity and procedure and conducts the first portion of

**Figure 1:** Initial Surgical Safety Checklist developed at CCTH (February 2016)

| **PATIENT DETAILS**<br>Last name:<br>First name:<br>Date of birth:<br>Folder number:<br>Procedure:<br><br>**BEFORE INDUCTION OF ANAESTHESIA (with at least nurse and anesthesia)**<br><br>Has the patient confirmed her identity, procedure and consent? ☐<br>Is the anaesthesia machine and medication check complete? ☐<br>Is the pulse oximeter on the patient and functioning? ☐<br>Are there any allergies? Yes No<br>Is there a difficult airway or aspiration risk? Yes No<br>If yes, is there equipment/assistance available? ☐<br>Is there a risk of >500ml blood loss? Yes No<br>If Yes, is IV access adequate and is the patient crossmatched? ☐ | **BEFORE SKIN INCISION**<br>**Quiet Time-Out**<br>**(Nurse, anaesthetist and surgeon)**<br><br>Has the patient's name, procedure and incsion site been confirmed? ☐<br>Have all team members introduced themselves by name and role? ☐<br>Are there any allergies?<br>Has antibiotic prophylaxis been given within the last 60 minutes? Yes Not applicable<br>How long will the case take?<br>Is there a risk of >10cc/kg of blood loss? Yes No<br>If yes, is the patient crossmatched? Yes No<br><br>Are there any patient-specific concerns?<br><br>Are there any anticipated critical events? Yes No<br>If yes, wehat are they?<br><br>**To Nursing Team:**<br>Are the packs sterile? ☐<br>Are there any equipment issues or any concerns? Yes No | **BEFORE PATIENT LEAVES OPERATING ROOM**<br>**(Nurse, anaesthetist and surgeon)**<br><br>Name of th eprocedure confirmed<br>Instrument, sponge and needle counts completed ☐<br>Specimen labelled (read specimen labels aloud, including patient name) ☐<br>Are any equipment problems to be addressed? Yes No<br>If yes, please specify:<br><br>Does the patient need transfucion postopertaively? Yes No<br>If yes, is the patient crossmatched? Yes No |
|---|---|---|
| **Specific to Cesarean Section:** | | |
| Is fetal heart beat present? Yes No | Is tubal litigation to be performed? Yes No<br>Is cord blood necessary? Yes No | |

**DATE (DDMMYY):** _____ **NAME:** _____ **SIGNATURE:** _____

the checklist), before skin incision (the surgeon conducts the second portion of the checklist), and before the patient leaves the operating room (the circulating nurse finalises the checklist). After the checklist was piloted, changes were made to further adapt the content to CCTH. The resulting SSCL is shown in Figure 1.

The checklist was then used by CCTH clinical staff as part of usual clinical care for all surgical patients and was printed on the back of surgical sponge count sheets, which were present already in all surgical cases, to facilitate its use.

*Measures:* To assess the use of the SSCL after its introduction, a post-implementation review of randomly selected surgical charts was conducted from November 2016 to November 2017. Approximately 300 surgeries were performed per month at CCTH in 2016. In order to not overwhelm the evaluation team, but to create enough knowledge of the process of implementation, we set out to audit the use of the SSCL in approximately 2.5% of cases per month over a 12-month period, which would amount to approximately eight cases per month.[7] In 2016, 1113 caesarean deliveries were performed at CCTH.[2] As part of our audit, we set out to evaluate 2.5% of caesarean deliveries, amounting to 2-3 charts per month over a 12 months period.

The Kybele team also observed four additional cases after implementation of the checklist (in November 2017) and documented qualitatively any deficiencies in adherence. A load of four cases was felt to be realistic in the context of the short visits by the Kybele team and the breadth of the Kybele mission (thus limiting the human and time resources that can be dedicated to a single project). Two members of the Kybele team (AM, VR) directly observed the four cases and recorded how the SSCL was used in real time.

*Ethical approval:* Approval of this quality improvement project was provided by the Cape Coast Teaching Hospital Ethical Review Committee on November 30th, 2017, reference number CCTHERC/RS/EC/2017/47. Informed consent was not required as this was part of a quality assurance activity.

*Funding:* This quality improvement activity is part of an ongoing collaboration between Kybele Inc. and CCTH to reduce maternal and neonatal mortality. No additional funding was contributed for this project specifically.

*Analysis:* Use of the SSCL was evaluated and the results calculated as percentage of charts where the SSCL was present and percentage of charts where the SSCL was present and complete. The incomplete SSCLs were then evaluated in order to distinguish if particular parts of the SSCL are more likely than others to be utilized.

Among those charts where the SSCL was incomplete, we examined each critical point in time (before induction of anesthesia, before skin incision, before the patient leaves the theater). Completion at each of these critical times was calculated as percentage of those charts where the checklist was used but was incomplete. Statistical significance was determined using McNemar's test for dependent proportions, with a p-value less than 0.05 representing statistical significance. The most common areas of missing information were assessed and the results shown as percentage of cases where the SSCL was present on the chart but was incomplete.

## Results

We randomly selected 120 chart numbers to audit, of which 20 charts were missing. We evaluated the use of the SSCL in 100 total surgical charts, which met our criteria of approximately 2.5% of surgical cases. Out of these, 28 were caesarean deliveries, which also met our criteria of 2.5% of caesarean section cases, and the rest were a mix of surgical specialties including general surgery (24 cases), otolaryngology (12 cases), urology (12 cases), orthopedic surgery (12 cases), and other (plastic surgery, ophthalmology, neurosurgery for a total of 24 cases). The chart review included both elective and emergency surgeries.

The SSCL was present on 93% (95% CI 88%-98%) of the charts, 92.9% (95% CI 83.5%-102.5%) of C-sections and 93.1% (95% CI 87.1%-98.9%) of non-C-section charts. It was complete in only 21% (95% CI 10.5%-29.0%) of cases, which included 3.6% (95% CI -3.3%-13.0%) of Cesareans and 27.8% (95% CI 17.5%-38.1%) of non-Cesareans cases.

We analyzed the charts where the checklist was present but incomplete. In those cases, Part 1, conducted before induction of anesthesia, was complete in 31.9% of cases (95% CI 21.2%-42.7%; n=72). Part 2, conducted before skin incision, was completed in 34.7% (95%CI 23.7%-45.7%). Part 3, before the patient leaves the operating theater, was complete in 65.3% of cases (95% CI 54.3%-76.3%). While there was no difference between completion rates of

**Table 2:** Utilization of the SSCL when it was incompletely filled out

| | Part 1 (Before Induction of Anaesthesia) | Part 2 (Before Skin Incision) | Part 3 (Before leaving the theater) |
|---|---|---|---|
| All cases (N=72) | 31.9% (21.2%-42.7%) | 34.7% (23.7%-45.7%) | 65.3% (54.3%-76.3%)* |
| C-sections (N=25) | 28.0% (10.4%-45.6%) | 28.0% (45.6%-10.4%) | 68.0% (49.7%-86.3%)* |
| Non C-sections (n=47) | 34.0% (20.5%-47.6% | 38.3% (24.4%-52.2%) | 63.8% (50.8%-76.9%* |

[a]Proportions represent number of cases where the checklist was filled out at a critical point divided by cases where the checklists was present on the chart but incomplete and shown as n% (95% CI)

*p<0.05 (McNemar's test for dependent proportions)

Part 1 and Part 2, Part 3 was significantly more likely to be completed than either Part 1 (OR 3.0, 95% CI 1.5-5.8) or Part 2 (OR 4.1, 95% CI 1.8-9.4). This trend persisted when we analyzed Cesareans and non-Cesarean cases separately (Table 1).

The most common themes in incomplete charts are shown in Table 2. Date of birth was not completed most often. Critical information such as estimated blood loss, antibiotic prophylaxis, documentation of allergies, patient specific concerns and need for postoperative transfusion was also found to be incomplete.

The Kybele team directly observed four randomly selected cases (two cesarean sections, a limb amputation and a nephrectomy) and documented qualitatively how the checklist was conducted. It was found that the checklist was not conducted at the appropriate pause times in the case. Additionally, not everyone paused to attend to the checklist. Some checklist items were filled out on paper without actual verbal communication about it amongst team members. Often, the surgeon would leave the theater before Part 3 was completed. These findings were consistent across the cases observed.

## DISCUSSION

*Summary:* This study illustrates a model of implementation of a WHO adapted surgical safety checklist at an academic referral hospital in West Africa. The staff were provided with information and training and subsequently a locally-developed checklist was introduced. The local staff took on an active role in the development and distribution of the checklist and printed it on the back of sponge count sheets which were already present on all surgical charts, making the SSCL more convenient and cost-effective. Subsequently, we found high uptake of the SSCL on the charts reviewed. Unfortunately, we found that in most cases the SSCL was not complete and adherence in practice was suboptimal.

An important strength of this project was the involvement of the local team in its development and implementation. In addition, charts were selected randomly over a year which provided a more accurate representation of its true use. Selecting charts from a shorter period of time just before or during a visit by the Kybele team may have led to an overestimation of its use. Lastly, evaluating 2.5% of surgical charts randomly did not overwhelm the evaluation team and allows for a process of continuous evaluation by the local staff even after the collaboration with Kybele concludes.

*Interpretation:* The high uptake on charts was probably largely due to local Anesthesia leadership, who oversaw that the physical checklist was added to the charts. Unfortunately, in most of these, the SSCL was incomplete. Particularly in Cesarean sections, the SSCL was complete in only 3.6% suggesting that there was little buy in from the surgical team. Cesareans are the most common surgery performed at CCTH. In the two emergency Cesareans we reviewed, the SSCL was not present on the chart. We discussed this finding with the obstetrical team, who felt that in an emergency setting there is no time to do the checklist. With ongoing education and use, the perception around the time commitment to do the SSCL, and its importance especially in emergency or complex cases, will become more apparent and will lead to improved utilization over time.

When the SSCL was used suboptimally, it was Part 3 that was most likely to be filled out (before the patient left the operating room). Observation of four randomly chosen cases showed that the surgeon often left the room first and the checklist was done by the circulating nurse. It is possible that the circulating nurse felt more comfortable requesting the attention of the room after the surgeon left, alluding to hospital hierarchy as a possible barrier to proper use. Other contextual factors may have contributed to this finding, including lack of familiarity with the SSCL, a perception that the SSCL is not important, and time pressures. The exact wording and cultural relevance of the SSCL may also have been a factor. We explored the themes that were incomplete most often and altered the SSCL based on the results of this QI initiative, in order to improve compliance. Date of birth was missing in 35% of total surgical charts evaluated. Recording patient demographics ensures that the procedure is done on the correct patient. At CCTH, many patients may not know their date of birth, therefore the local partners suggested replacing this item with age. Critical considerations such as estimated blood loss and patient specific concerns were frequently missing in surgical charts.

**Table 2:** Themes in Incomplete Charts

| Theme | N charts | % of charts* |
|---|---|---|
| Date of birth | 33 | 35% |
| Other identifying patient information | 20 | 22% |
| Estimated blood loss | 22 | 24% |
| Patient specific conerns/anticpated critical events | 11 | 12% |
| Equipment concerns | 11 | 12% |
| Antibiotic prophylaxis | 9 | 10% |
| Specimen labelling | 8 | 9% |
| Sterile packs | 6 | 6% |
| Need for postopertaive transfusion | 4 | 4% |
| Postoperative conerns | 3 | 3% |

*Percentages are calculated as proportion of total surgical cases where the checklist was present on the chart

Antibiotic prophylaxis was often not documented, a relevant point at CCTH where 26% of maternal deaths are attributed to sepsis [8]. Estimated blood loss was missing in 24% of evaluated charts. It was felt that a more clinically relevant question would be: "Is there a risk of excessive blood loss?". Whether there were patient specific concerns and/or anticipated critical events was not documented in 12% of charts evaluated. They were listed as two separate items, both prior to skin incision, and the local team felt that this was redundant. The item "Are there any anticipated critical events?" was removed. Specimen labelling was not documented in 9% of charts. To ensure this item was checked even in surgeries where a specimen was not sent to pathology, the answer option for this question was changed to include a checkbox for "not applicable". Lastly, the checklist was reformatted to allow for more writing space when postoperative concerns are identified before the patient leaves the room. The revised SSCL is shown in Figure 2. Using this QI project as template, an evaluation team was developed that will periodically assess how the SSCL is used and adjust it as needed to better serve the local patient population after the collaboration with Kybele concludes.

The WHO Surgical Safety Checklist has been adopted in a number of hospitals across the world however most reports come from upper middle and high-income countries.[9,10,11,12,13,14,15] Few studies report on its implementation in low income settings. White et al. (2017) reported on a four-day pilot to implement the SSCL at Dolisie Hospital in the Congo.[16] They were unable to evaluate uptake but commented that the most important barriers to implementation were lack of support and differences between training and actual surgical milieu. At Felege Hiwot hospital in Ethiopia, Ellis et al. (2017) implemented a stepwise SSCL program that resulted in an uptake rate of 94% in general surgery cases and 100% in OBGYN cases at one year.[17] Similar to our project, their strategy was also locally driven, and the authors identified local support as one of the key components of a successful program. A prospective study of elective general surgeries in Karachi, Pakistan showed checklist use in 20% of cases at 1 year. At four years, use increased to 90%.[18]

The literature on implementation of a surgical safety checklist in LMICs is sparse. However, existing studies typically found high uptake, in keeping with our results. But to be effective, the SSCL must not only be present, but must be fully completed, at the appropriate times in the surgical process, by the appropriate members of the surgical team and there must be real time communication prior to checking it off. When problems are identified, the SSCL should trigger a management plan. Further research is needed on compliance with the checklist in real time and on strategies to improve adherence and patient outcomes.

**Figure 2:** Revised surgical safety checklist (November 2017). The modified sections based on local feedback are highlighted

| **PATIENT DETAILS**<br>Last name:<br>First name:<br>Age:<br>Folder number:<br>Procedure:<br><br>**BEFORE INDUCTION OF ANAESTHESIA (with at least nurse and anesthesia)**<br><br>Has the patient confirmed her identity, procedure and consent? ☐<br>Is the anaesthesia machine and medication check complete? ☐<br>Is the pulse oximeter on the patient and functioning? ☐<br>Are there any allergies? Yes No<br>Is there a difficult airway or aspiration risk?<br>Yes No<br>If yes, is there equipment/assistance available? ☐<br>Is there a risk of excessive blood loss? Yes No<br>If Yes, is IV access adequate and is the patient crossmatched? ☐ | **BEFORE SKIN INCISION**<br>**Quiet Time-Out (Nurse ,anaesthetist and surgeon)**<br><br>Has the patient's name, procedure and incsion site been confirmed? ☐<br>Have all team members introduced themselves by name and role? ☐<br>Are there any allergies?<br>Has antibiotic prophylaxis been given within the last 60 minutes? Yes Not applicable<br>How long will the case take?<br>Is there a risk of excessive blood loss? Yes No<br>If yes, is the patient crossmatched? Yes No<br><br>Are there any patient-specific concerns?<br>If yes what are they?<br><br>**To Nursing Team:**<br>Are the packs sterile? ☐<br>Are there any equipment issues or any concerns? Yes No | **BEFORE PATIENT LEAVES OPERATING ROOM (Nurse, anaesthetist and surgeon)**<br><br>Name of th eprocedure confirmed<br>Instrument, sponge and needle counts completed ☐<br>Specimen labelled (read specimen labels aloud, including patient name) Yes NA<br>Are any equipment problems to be addressed? Yes No<br>If yes, please specify:<br><br>Are there any concerns in the immediate postoperative period? Yes No<br>If yes, please specify:<br><br>Does the patient need transfucion postopertaively? Yes No<br>If yes, is the patient crossmatched? Yes No |
|---|---|---|
| **Specific to Cesarean Section:** | | |
| Is fetal heart beat present? Yes No | Is tubal litigation to be performed? Yes No<br>Is cord blood necessary? Yes No | |

**DATE (DDMMYY):** _____ **NAME:** _____ **SIGNATURE:** _____

*Limitations:* This is a small QI activity with inherent limitations. In order to maintain a feasible process of evaluation while extracting useful information, only 2.5% of surgical charts were evaluated, including 2.5% of caesarean section charts. Ideally, more charts would be audited and more cases would be directly observed. However, evaluating 100 charts and four surgical cases did help delineate important patterns in the SSCL process and ultimately guided how it would be used in the future.

We were only able to evaluate how the checklist was conducted in four cases due to the nature of the Kybele biannual trips. This is a limitation of our project. However, these cases were randomly chosen without advanced notice in order to capture normal behaviour as much as possible. A possible Hawthorne effect cannot be excluded however it is important to note that even when directly observed, the surgical team did not implement the checklist appropriately. Some items were checked off without being communicated thereby not taking advantage of the intended usefulness of assuring readiness at each critical point. To address this important deficiency, the Kybele team presented this information to stakeholders including OBGYN staff, medical and house officers in November 2017 with the goal of improving real time adherence.

*Conclusions:* This quality improvement activity demonstrated a model of implementation of the SSCL in an under-resourced area where it had not been used before. A key aspect in SSCL program development is local leadership and multidisciplinary support. The SSCL represents a low-cost strategy to reduce surgical morbidity and mortality but current literature is lacking in reports of its implementation in LMICs. The CCTH model can be adapted in other settings to introduce the SSCL, monitor its utilization over time, develop a data collection system and enhance surgical care without placing undue burden on local resources. We encourage researchers in LMICs to use the current model or develop new strategies of implementation of the SSCL and to report on their findings.

*Authors contributions:* AM, MM, HT, RG, HS and VR contributed to all aspects of the design. AM had overall responsibility for this project and VR had supervising responsibility. AM and VR conducted the data analysis. RG coordinated the collaboration between CCTH and Kybele Inc., including this project. MM, HT, BQ and NA developed the SSCL and coordinated its printing and distribution. All authors gave approval for the final version of the manuscript.

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Update in
Anaesthesia

Research

# Post-operative pain management at Hospital Nacional Guido Valadares, Dili, Timor-Leste

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**Abstract**

After decades of turmoil Timor-Leste is re-building its healthcare system. Resource limitations are severe. Opiates are unavailable on the wards and used sparingly in theatres. Minimal staff training, inadequate medication supply and cultural acceptance result in poor pain management. This audit examines post-operative pain management in 85 patients thought reasonably to require post-operative analgesia. Despite medication being charted 20 patients (24%) received no post-operative analgesia, (before review). This group had a mean verbal numeric pain score of 5.8+/-2.2, median 6, range 2-9. Thirty-four patients (41%) received some of their charted analgesics. This group had a mean pain score of 5.1+/-2.2, median 5, range 1-9. The remaining 31 patients received their analgesics as charted and, unsurprisingly, had the lowest pain scores, mean 4.3+/-2.3, median 4, range 1-8. No patient received prn analgesia. More than 40% of patients reported pain scores greater than 5, with 15% reporting pain scores of 8 or 9. Forty-seven patients (55%) were unsatisfied with their pain relief. Fifty-one patients (60%) received additional analgesia as a result of review. Despite cultural expectations Timorese patients would welcome additional post-operative analgesia. To achieve this there are significant hurdles to overcome in training, drug availability and attitudes towards pain relief.

## INTRODUCTION

Following decades of occupation, warfare and political turmoil The Democratic Republic of Timor-Leste became a sovereign nation in 2002. In the years immediately prior to this virtually all the country's infrastructure was damaged. Government institutions were destroyed or ceased to function. The health sector was no exception. The country had few trained doctors or nurses. Hospitals and Health Centres were run down, poorly funded and many simply unstaffed. Government revenue was, and remains, minimal. Timor-Leste is reported to spend less than any other country on healthcare with only 2.4% of government revenue reserved for health.[1] Post-independence the government urgently needed medical officers and large numbers of medical students were sent to Cuba for training . This has been a mixed blessing. Cabral et al in their article stress that such scaling up of numbers is not in itself enough . Junior medical staff require ongoing training. These medical graduates have come back with minimal clinical experience and receive limited or no mentorship on their return. High quality nursing staff are also in desperately short supply. The standard of nurse training is low. Opiates are unavailable on the ward. Discussion with staff suggests there is an unrealistic fear of the dangers of opioid use, in particular respiratory depression and addiction. Tramadol, paracetamol and ibuprofen in various combinations are the backbone of post-operative analgesia. Unfortunately anecdotal clinical observation also suggests there is an unrealistic fear of the consequences and frequency of paracetamol overdose, with the standard adult dose charted as 500mg tds. Medications are frequently not administered so patients are not only under prescribed but miss doses as well. All this leads to poor post-operative pain management. However it is within the current capability of the Hospital Nacional Guido Valadares (HNGV) to improve on this situation. It is with this in mind and a view to teaching and decreasing the level of unnecessary suffering that the following audit of post-operative pain management in HNGV was undertaken.

## METHODS

Over a 3 month period, (following institutional approval), consecutive general, urological, gynaecological and orthopaedic patients 17 years and older were selected for review of their post-operative pain management. Patients were selected pre-operatively on the basis that their surgery was thought reasonably likely to require post-operative analgesia. Emergency and elective cases were included but each patient was only reviewed once. There was no upper age

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limit. Patients were not selected for a single anaesthetist or surgeon, i.e. all patients were eligible for review regardless of the anaesthetist or surgeon. The caring anaesthetist recorded details of the anaesthesia and analgesia given intra-operatively. In recovery patients were asked to verbally rate their pain (0 being no pain at all, 10 being worst pain imaginable). The result was recorded by recovery staff as soon as practicable on arrival and then again immediately prior to departure for the ward. On the first post-operative morning between 10 and 12 o'clock a single observer (author) visited each patient on the ward with a local medical officer interpreter. The latter varied depending on the day. Each patient had a record kept. This comprised basic demography, the procedure, the nature of anaesthesia, (spinal vs general), details of duration and analgesics given in theatre and recovery, pain score in recovery and details about post-operative analgesics charted. The following morning each patient was attended as above. They were again asked to verbally rate their pain on a numeric scale between 0-10. Patients were also asked if they were satisfied with their pain relief and if they would like more pain relief. The patient's ward chart was also inspected to see if they had been administered analgesics as charted, this was corroborated with the patient and staff where possible. Where appropriate results are reported as mean +/- standard deviation.

## RESULTS

Eighty-five patients were reviewed; 47 males,38 females. The mean age was 36.4 +/- 16.6 years. 48 patients were general surgical, 12 orthopaedic, 14 urological, 10 gynaecological and 1 maxillofacial. Table 1 contains the operative procedures. Operative time was recorded for 49 cases; mean 105+/-50mins.

Forty cases (47%) were performed under spinal anaesthesia. Of these 5(12.5%) used intrathecal fentanyl. Thirteen spinals (32.3%) required supplementation with intravenous ketamine and 4(10%) were converted to general anaesthesia.

Forty-five cases were performed under general anaesthesia with all but 4 using fentanyl. The mean fentanyl dose was 102.8+/-38.5mcg. Rarely did a patient receive a second dose of intra-operative fentanyl. Thirty-two (80%) of the general anaesthetic cases were given intravenous morphine. The mean morphine dose was 6.1+/-3.5mg. Thirteen cases reported lignocaine infiltration into the surgical wound.

Overall the mean analogue pain score on arrival in recovery was 3.3+/-2.6. For patients post spinal anaesthesia mean recovery pain score was 2.4+/-2.5. For patients post general anaesthesia recovery pain score was 4.2+/-2.5. Thirty-six patients (42%) received analgesia in recovery. Twelve received morphine, mean dose 5.8+/2.8mg. Twenty-three received tramadol, of which 95% was 100mg intramuscularly. Prior to ward discharge the overall mean pain score was 3.0+/-2.1.

On review the following morning overall mean pain score was 5.0+/-2.2, median 5, range 1-9. Table 2 contains the frequency distribution of pain scores. More than 40% of patients reported pain scores greater than 5, with 15% reporting pain scores of 8 or 9.

Of the patients post spinal anaesthetic mean pain score the next day was 4.7+/-2.2, median 5, range 1-9. For patients post general anaesthetic mean pain score was 5.2+/-2.2. As a result of review 17(43%) of the post-spinal anaesthetic patients 17(43%) and 28(62%) of the post general anaesthetic patients were given additional pain relief.

No patient was given prn analgesia prior to review. Table 3 shows next day pain scores for patients given their analgesics either as charted, partially or not all. It was observed that many patients were fasted 6 hours post-operatively, whether they needed it or not. Additionally in the face of nausea nursing staff were frequently observed to withhold analgesia but not provide alternative pain relief. Both these situations led to further incidences of missed oral analgesics.

Overall 47 patients (55%) were unsatisfied with their post-operative pain relief. Fifty-one (60%) received additional analgesia as a result of post-operative review.

## DISCUSSION

This is one of the first papers involving direct clinical observation of acute care patients to come out of Hospital Nacional Guido Valadares (HNGV). Its completion was challenging. Patients and staff were unfamiliar with the research process and required education, encouragement and reassurance. Additionally, as has been known for many years and highlighted by many authors, pain, its expression and treatment are heavily influenced by culture. Peacock and Patel summarize this: "A cultural group's expectations[4,5,6] and acceptance of pain as a normal part of life will determine whether pain is seen as

**Table 1:** Operative Procedures

| Procedure | Count |
|---|---|
| Appendicectomy | 19 |
| Laparotomy | 14 |
| Major Open Urological | 14 |
| Miscellaneous | 9 |
| Major ORIF Lower Limb | 8 |
| Abdominal Hysterectomy | 5 |
| Open Inguinal Hernia | 5 |
| Open Cholecsytectomy | 4 |
| ORIF Upper Limb | 3 |
| Mastectomy | 2 |
| Thoracotomy | 1 |
| Thyroidectomy | 1 |

**Table 2:** Pain Score Day One Frequency Distribution

| Pain Score Day 1 | Frequency |
|---|---|
| 1 | 3 (3.6%) |
| 2 | 13 (15.5%) |
| 3 | 8 (9.5%) |
| 4 | 13 (15.5.%) |
| 5 | 13 (15.5.%) |
| 6 | 10 (11.9.%) |
| 7 | 11 (13.1.%) |
| 8 | 8 (9.5.%) |
| 9 | 5 (5.9.%) |

**Table 3:** Pain score day one vs Analgesic Medication Given As Charted

| Charted Analgesic Medication Given | Pain Score Mean+/-StDev | Pain Score Median, Range | Extra analgesia Given on review |
|---|---|---|---|
| **No** | 5.8+/-2.2 | 6, 2-9 | 85% |
| **Partially** | 5.1+/-2.2 | 5, 1-9 | 85% |
| **Yes** | 4.3+/-2.3 | 4, 1-8 | 65% |

a clinical problem". Further they suggest, "The relationship between pain and ethnicity is shaped by experience, learning and culture". The comparatively recent experience of the Indonesian occupation,[7] the war of resistance and the violence around independence and again in 2006 mean that nearly everyone in Timor-Leste has a story; everyone has suffered and acceptance of pain as a part of life is commonplace. The incidence of post-traumatic stress disorder amongst the general population is reported to be high.[8,9] All this manifests itself in the attitudes of patients and staff at HNGV towards pain.

However, this is just part of the background to the cultural approach to pain in Timor-Leste. Medical personnel are held in high esteem and there is a significant power imbalance between patients and staff. Interpreters were able to provide several comments in this regard. Examples include "They (patients) are afraid that you will keep them in hospital," or "They do not want to ask in case they get in trouble" or "They do not want to appear weak". Similarly nursing staff when requested if they could provide more analgesia for a patient would frequently state, "They have already had pain relief", as if to say a single dose of analgesia was all the patient required and would last the entire post-operative period. The observed common practice of fasting patients post-operatively, and withholding analgesia in the presence of nausea led to further incidences of missed oral analgesics. Overall these factors combined to produce the impression that patients in general under-reported the degree of pain they were experiencing. Even so more than half the patients reported being unhappy with their post-operative analgesia and 60% received additional pain relief as an outcome of their review.

Spinal anaesthesia is the first option for anaesthesia at HNGV. It is cheap and requires minimal equipment. In recovery these patients did marginally better from a pain perspective than those who underwent general anaesthesia. This trend appeared to continue through to the following day. However this likely reflects the nature of the surgery performed under spinal rather than the nature of the anaesthesia. For example lower limb fractures etc can be performed under spinal and are likely to be better tolerated post-operatively than major laparotomies, or cholecystectomy which require general anaesthesia. A third of spinals required supplementation with ketamine towards the end of the procedure and a tenth were converted to general anaesthesia. These findings suggest that spinals are potentially being used in situations where a general anaesthetic may be more desirable.

Within operating theatres opiate use was sparing. Regardless of the length, size or nature of the procedure 100mcg of fentanyl was the standard dose. This suggests there is little titration of opioid to the clinical circumstances. For those undergoing general anaesthesia the mean morphine dose was 6mg. Plain bupivacaine is not available at HNGV. Lignocaine infiltration of the surgical wound was a relatively new concept and employed sparingly. Forty-two percent of patients received analgesia in recovery but only 14% received morphine. Intramuscular tramadol was the recovery analgesic of choice. For those in severe pain post-operatively intravenous opioids would likely be a better choice.

Once patients left recovery and returned to the wards opiates were unavailable. On the one hand this indicates what can be achieved, managed or maybe just tolerated with tramadol and paracetamol, and some ibuprofen. On the other hand it reflects on the likely unmet need for strong analgesics on the ward. One in seven patients reported pain scores of 8 or 9. The frequency of tramadol use was surprising as it represents a more expensive option than most opioids.

The biggest finding was the frequency with which patients were receiving no analgesia whatsoever on the ward. "As required" analgesia is also a concept that is not embraced. This may be due to perceived powerlessness amongst nursing staff and/or lack of education. Nearly a quarter of patients received no analgesia post-operatively. The causes of this are complex. Some are attitudinal and educational as discussed above, some are a failure in nursing care standards and finally some are logistic. Getting medication to the ward is unnecessarily complex; the wards do not hold impress and have to procure medication from pharmacy for each patient. Sadly all the above are common in low to middle income countries.

At HNGV the responsibility for prescription of post-operative analgesia rests with the surgical team. Doses prescribed are often low and inappropriately infrequent, for example the observed standard charted adult paracetamol dose is 500mg tds. Provided this is given it is probably better than nothing. However as the local experts it would seem appropriate that anaesthetic staff take over responsibility for prescribing post-operative analgesia.

Myles et al suggest that a visual analogue pain scale of 33 or less on a 100mm scale signifies acceptable pain after surgery.[10] There is no immediately apparent reason to suggest that verbally reported pain scores should be any different. The mean pain score on review here was 5.0, with 71% of patients reporting pain scores in excess of 3. Fifty-five% of patients reported being dissatisfied with their pain relief. Given the likely cultural bias towards underreporting this figure is at least comparable and provides some vindication of the accuracy of the findings.

In its simplest interpretation this audit highlights that patients given analgesia have less pain than those who aren't given analgesia. So what potentially can be done to improve the delivery of analgesia? Paracetamol, ibruprofen and morphine are all relatively cheap. Nursing staff are available. Surgical and medical staff are present and operating. As highlighted by Morriss and Roques "there is a treatment gap (in low to middle income countries) between what could be done and what is actually being done. Because of this gap, there are many opportunities

to dramatically improve pain management using simple, cost-effective strategies."[11] This is the case at HNGV. All the elements for improved post-operative pain management are present but they do not translate into better analgesia for patients. Potential recommendations for improvement might include:

1) Education of resident medical and nursing staff on the importance of pain relief, dispelling unrealistic fears associated with analgesic use and instruction on the appropriate dosing regimens of common analgesics; in particular changing from paracetamol 500mg tds to 1gm qid for normal sized adults.
2) Improved processes for impress on the wards
3) Anaesthetic staff to have a lower threshold for increased opiate use in theatre and recovery
4) Anaesthetic staff to take over prescription of post-operative analgesia
5) Education regarding the unnecessary practice of post-operative fasting
6) Daily post-operative pain rounds by the anaesthetic team.

The institution of such measures is not easy but even some progress will decrease the amount of unnecessary suffering amongst Timorese patients at HNGV. The International Association for the Study of Pain (IASP) has called 2018 the Global Year of Excellence in Pain Education.[12] It is hoped that conduct of this audit has been an educational opportunity for at least some of the staff at HNGV and opened the door for change. Visiting International teams have an educational role to play in this regard as well. Attention to post-operative analgesia and education on post-operative pain by visiting surgical teams will go some way to combatting culturally held myths at HNGV and help provide a lasting legacy in the form of improved pain management for the people of Timor-Leste.

The standard of post-operative pain management at HNGV is low. The findings presented here suggest approximately 70% of patients are experiencing a level of post-operative pain greater than that recommended as acceptable.[10] Despite cultural expectations the results indicate that Timorese patients would welcome additional post-operative pain relief. The capacity for improvement is there with significant hurdles to be overcome in training, drug availability and general attitudes towards post-operative pain relief.


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Update in
Anaesthesia

Review

# Comprehensive Review of Laryngospasm

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**Abstract**

Laryngospasm is a well-known entity occurring during the perioperative period, most commonly during intubation or extubation. Clinical signs are the consequence of patient effort to breath against a closed glottis.

Risk factors can be related to patient, surgery or anesthesia. They should be managed pre-operatively in order to prevent this occurrence, together with preventative drugs such as iv (intravenous) lidocaine and magnesium sulphate, iv propofol induction instead of the inhalational route in children and laryngeal aspiration before extubation.

Prompt diagnosis and management is the key to success and includes Continuous Positive Airway Pressure (CPAP) with 100% oxygen, manual maneuvers (subluxation of the temporomandibular joint and Larson's maneuver), increasing depth of anesthesia and muscle relaxation. If these measures do not succeed, forced orotracheal intubation or even cricothyroidectomy/tracheostomy are the emergency steps

## INTRODUCTION

Perioperative laryngospasm is a life threatening complication during the perioperative period with an incidence of 0.78-5% depending on the surgical type, patient age, pre-existing conditions and anesthetic technique.[1]

It is defined by a sustained closure of the vocal cords as a primitive protective airway reflex to prevent tracheobronchial aspiration after an offending stimulus. The prolongation of this initial beneficial reflex after the stimulus has ceased, results in inadequate ventilation due to airway obstruction. It occurs most frequently during intubation or extubation due to a superficial level of anesthesia.[2]

The diagnosis can only be made if the closed glottis and vocal cords are visualized which is not possible in the great majority of cases. So usually it depends on the anesthesiologist's clinical judgement. Clinical signs include inspiratory stridor, paradoxical respiratory movements, suprasternal and supraclavicular retractions and rapidly decreasing oxygen saturation. As the obstruction progresses to a complete airway obstruction, the chest movements may be excessive but there is no movement of the reservoir bag and no capnogram reading. Desaturation is the most common manifestation. Other manifestations are bradycardia (6%), negative pressure pulmonary oedema (4%), cardiac arrest (0.5%), pulmonary aspiration (3%), arrhythmias and death.[3]

It is important to exclude other differential diagnoses such as: bronchospasm, supraglottic obstruction, psychogenic cause in anxious patients, vocal cord palsy, tracheomalacia, hematoma, foreign body, laryngeal edema or tracheal collapse.

## PATHOPHYSIOLOGY

Causes of laryngospasm may be mechanical, chemical or thermal occurring around the glottis. They trigger the afferent fibers of the internal branch of the superior laryngeal nerve. The receptors are distributed along the glottis with the majority found on the laryngeal surface of the epiglottis.

Innervation of the supraglottic region is by the superior laryngeal nerve, while below the vocal cords it is by the recurrent laryngeal nerve. They converge in the brainstem at the tract solitary nucleus, which plays an essential role in the genesis of the upper airway reflexes.

Lateral cricoarytenoids, thyroarytenoids and cricothyroids muscles (intrinsic laryngeal muscles) are responsible for adduction of vocal cords. All of them are innervated by the recurrent laryngeal nerve except the cricothyroid, which is supplied by the external branch of the superior laryngeal nerve. Their motor neurons are located in the ambiguous nucleus and adjacent to the retroambigualis nucleus which explains why stimulation of the upper airway mucosa

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also produces cardiovascular alterations (bradycardia, changes in arterial pressure) indicating that not only skeletal muscles but also smooth muscles are involved in these reflexes.[4]

During a laryngospasm episode, either true vocal cords alone or both true and false vocal cords can be involved.[5]

## RISK FACTORS

The actual known risk factors can be divided in three categories enumerated in Table 1.[6,7]

## PREVENTION

In order to reduce the incidence of laryngospasm, propofol induction is the best approach as it reduces the laryngeal reflexes, particularly in children with history of asthma.

It was proven that lidocaine 1-2mg.kg$^{-1}$ iv can be a preventive and corrective drug 2 minutes before extubation.[8] Topicalisation of the vocal cords with this agent has also been proven to be effective to prevent laryngospasm during general anesthesia in children.[9] Magnesium sulfate 15mg.kg$^{-1}$ iv before tracheal extubation has the ability to decrease airway reflexes and cough and may play a role in laryngospasm prevention.[10]

Another important measure is removing all secretions or blood until the larynx is completely cleared before extubation.

It is debated whether tracheal extubation should be performed in awake or deeply anesthetized patients to decrease laryngospasm.[11] The literature describes the "No touch technique" which comprises the extubation of a spontaneously breathing and awakening patient, without any kind of stimulation during the emergence from general anesthesia.[12]

The artificial cough maneuver has also been described as onesingle lung inflation with 100% oxygen immediately before the removal of the endotracheal tube. It delays/prevents desaturation in the first 5 minutes after extubation and expels residual secretions in the airway decreasing the potential for vocal cord irritation.[13]

## MANAGEMENT AND TREATMENT

The first step is to remove the laryngospasm stimulus, followed by a firm and vigorous mobilization of the jaw backwards with extension of neck and head, and apply CPAP with 100% oxygen via a face mask. The use of CPAP can inflate the stomach and increase the risk of gastric regurgitation. Some authors prefer the application of moderate intermittent pressure. Although airway devices can be a trigger for laryngospasm, a Guedel cannula of correct size may be helpful in providing CPAP.

Propofol in a subhypnotic dose of 0.25-0.8mg.kg$^{-1}$ iv usually breaks the spasm. If it does not, the next step is administration of succinylcholine 0.1mg.kg$^{-1}$ iv allowing preservation of spontaneous ventilation.[14] It has a quick onset because its ED95 is 0.3mg.kg$^{-1}$. Rocuronium also has an ED95 of 0.3 and will have as rapid an onset as succinylcoline and could be an option in patients who are not able to tolerate succinylcoline. Other drugs useful for treatment are alfentanil and meperidine, especially when the laryngospasm trigger was a painful stimulus. Doxapram 1.5mg.kg$^{-1}$ can suppress laryngospasm by increasing respiratory depth. Nitroglicerin 4mcg.kg$^{-1}$ has also been reported as effective but only acts on the smooth muscle and not on the skeletal muscle of vocal cords.[15]

The application of gentle pressure in the thoracic midline at a rate of 20-25 compressions per minute can reverse the spasm.[16] The real mechanism is unknown but some theories have been put forward. In the case of partial laryngospasm where only the true cords are involved, chest compressions will force the air through a small lumen left open at the posterior commissure of the vocal cords, ensuring ventilation and gas exchange and fast relief of partial laryngeal spasm.

**Table 1.** Known risk factors for larynogospasm

| Patient-related | Surgery-related | Anaesthesia-related |
|---|---|---|
| Obesity | Nasal, oral or pharyngeal surgeries (adenoidectomy and tonsillectomy) | Laryngeal mask/Guedel airway device |
| Young age | GI endoscopy | Extubation |
| Active and passive smoking | Bronchoscopy | Suction catheter |
| ASA IV | Appendicetomy | Light anaesthesia plan |
| Gastroesophageal reflux | Anal or cervical dilatation | Blood/secretions in the airway |
| Obstructive sleep apnoea | Mediastinoscopy | Regurgitation |
| Upper airway infection | Inferior urologic surgery | Desflurane |
| Hypocalcaemia | Skiin transplant | Ketamine and thiopental induction |
| Asthma | Nociception | Nasogastric tube |
| Difficult airway | Surgical stimulus | Inexperience of anaesthesiologist |
| | Movement | Failed intubation |
| | Recurrent laryngeal nerve damage | Laryngoscopy |
| | Esophageal stimulation | |
| | Iatrogrnic removal of parathyroid glands | |

In complete laryngospasm, in which both true and false vocal cords are opposed, this technique could help in converting to a partial spasm as air forced from below can push the area above the false vocal cords away from each other, opening the entrance of larynx. Another mechanism is the stimulation of the Hering-Breuer deflation reflex that, via the vagus nerve, may induce vocal cords relaxation.[17]

The second way is the so called Larson's Maneuver, with limited scientific evidence regarding its therapeutic use. It consists of bilateral pressure application on the mastoid processes at the level of styloid processes, between the posterior branch of the mandible and the anterior mastoid process. This results in laryngospasm cessation by provoking pain and relaxing the vocal cords.[18]

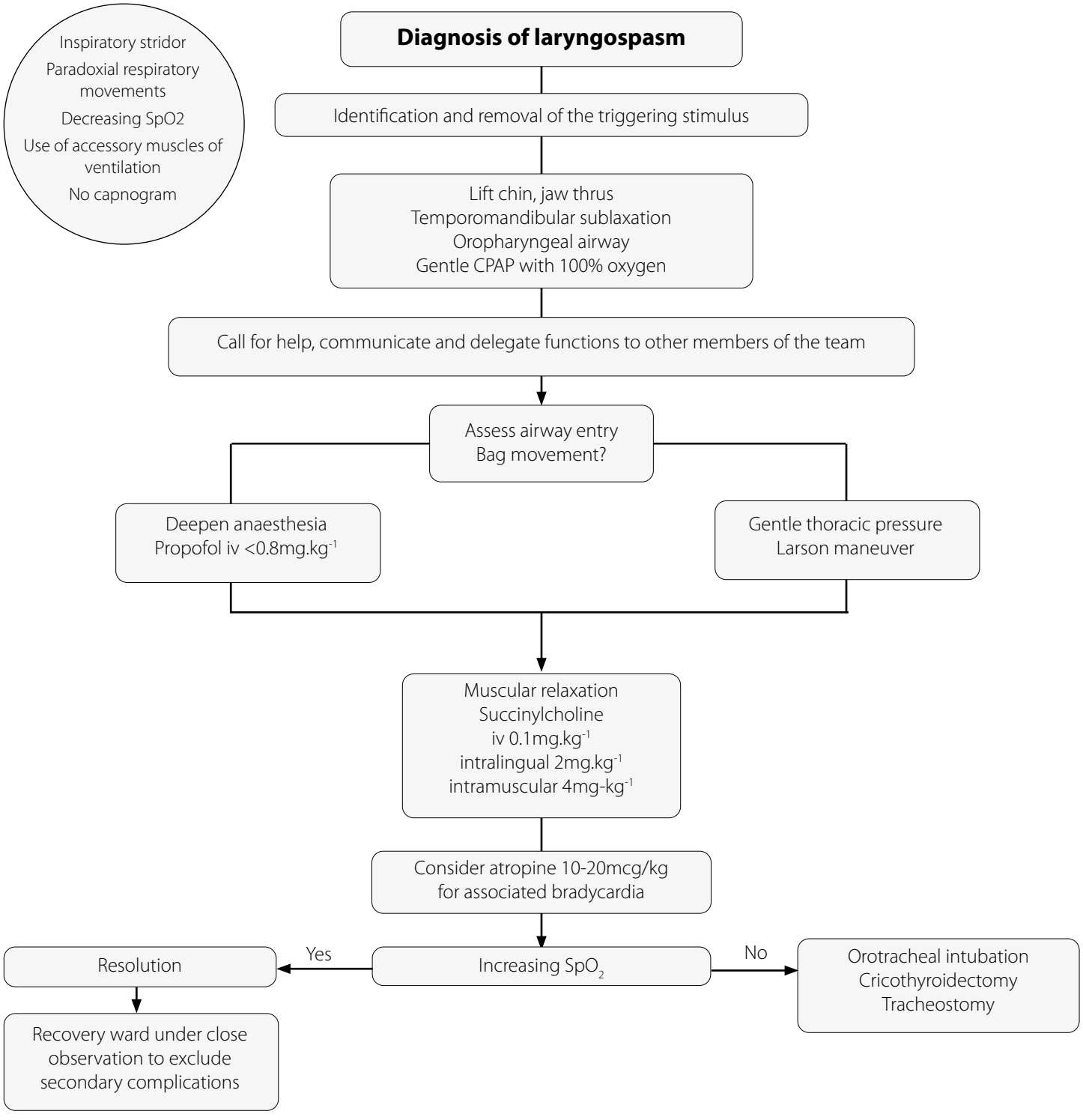


**Figure 1.** Simplified flowchart for laryngospasm management

One of the last measures is tracheal intubation, even with the vocal cords closed, producing trauma but rescuing the airway urgently. Cricothyroidotomy or tracheostomy are valuable procedures in extreme urgency. (Figure 1)

## FOLLOW-UP

These patients should be under observation for 2-3 hours in the recovery ward to confirm a clear airway and to exclude possible complications such as pulmonary aspiration and post-obstructive pulmonary oedema. This can be a particularly harmful consequence of marked negative intrathoracic pressures due to the airway obstruction and may require intubation, ventilation and management in an ICU.[1]

## CONCLUSION

Identifying risk factors and planning appropriate anesthetic management is the most rational approach to reduce laryngospasm incidence and severity.

When it occurs during the perioperative period, the priority is the prompt recognition and management according to a structured flowchart in order to minimize morbidity and mortality.

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Update in
Anaesthesia

Clinical Article

# Perioperative Myocardial Ischaemia in Non-cardiac Surgery

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## SUMMARY

- Perioperative myocardial ischaemia is an important entity with prognostic implications.
- Preoperatively, patients should have their perioperative risk clarified, and be optimised where time permits.
- Intraoperative management consists of appropriate monitoring and anaesthetic technique, preventing myocardial oxygen supply-demand imbalances and identifying and treating intraoperative myocardial ischaemia.
- Postoperative considerations will depend on intraoperative events and the risk category of the patient, but may involve intensive monitoring and cardiology review.

## Key Points

- Perioperative myocardial ischaemia may increase 30-day mortality when it results in myocardial infarction.
- Optimise at-risk patients preoperatively where time allows.
- Aim to match myocardial supply and demand intraoperatively and monitor for evidence of ischaemia during the perioperative period.

## INTRODUCTION

Myocardial ischaemia can proceed to myocardial infarction (MI), this is important as perioperative MI is associated with a significant increase in 30-day mortality.[1] This article will discuss preoperative, intraoperative, and postoperative strategies for prevention and management of perioperative myocardial ischaemia.

## PREOPERATIVE CONSIDERATIONS

### Risk-Evaluation Scoring Systems

Multiple scoring systems are available that predict the risk of major adverse cardiac events.[2] They tend to focus on a patient's past medical history and surgical risk factors. Lee's Revised Cardiac Risk Index is a simple, validated, and widely used scoring system that predicts major cardiac complications in major elective non-cardiac surgery[2]. The 6 independent factors are listed in Table 1.

Predicted cardiac event rate increases with increasing number of risk factors present, ranging from 0.4%-11%: 0 points- 0.4%; 1 point- 0.9%; 2 points- 6.6%; ≥ 3 points - 11%.[2]

Lee's cardiac risk index is only validated for elective surgery and does not encompass all risk factors for major adverse cardiac events. Of note, the outcome is a composite endpoint, not specific to myocardial

**Table 1.** The Lee Revised Cardiac Risk Index

| Criteria | Points |
|---|---|
| High-risk surgery (e.g., emergency surgery, major thoracic procedures, cardiac procedures, aortic/major vascular procedures, procedures . 4 hours) | 1 |
| Ischemic heart disease | 1 |
| History of congestive heart failure | 1 |
| History of cerebrovascular disease | 1 |
| Insulin therapy for diabetes | 1 |
| Perioperative serum creatinine >2.0mg/dL (>177lmol/L) | 1 |

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ischaemia or infarction. Other important risk factors include recent MI, recent insertion of coronary stents, elevated preoperative high-sensitivity troponin-I, valvular heart disease, decompensated heart failure, and arrhythmias. This article will discuss some of these risk factors in greater detail.

### Recent Percutaneous Coronary Intervention (PCI)

Subsequent to PCI, there is a known risk of in-stent thrombosis, which decreases with time after the procedure. In-stent thrombosis may result in myocardial ischaemia and is associated with a high mortality. In order to reduce this risk, patients are commenced on dual antiplatelet agents for the highest-risk period; the duration of therapy is specific to the type of stent placed.

Dual antiplatelet therapy increases the susceptibility to bleeding perioperatively. The risk of bleeding must be balanced against the risk of in-stent thrombosis relative to early cessation of antiplatelet agents. Because of these factors the 2014 American Heart Association/American College of Cardiology (AHA/ACC) guideline recommends that elective surgery be delayed (Table 2) and that urgent or emergency surgery have a multidisciplinary discussion regarding the risk and benefit of continuing or ceasing antiplatelet agents perioperatively.[3] Aspirin should be continued where possible.

### Recent MI

A recent MI increases the risk of perioperative MI and mortality.[4] As time since the MI occurred increases, the risk of reinfarction decreases. A retrospective study showed that the risk of reinfarction decreased from 32.8% when surgery occurred within 0-30 days of MI compared with 5.9% when surgery occurred 91-180 days post-MI.[4] The likelihood of reinfarction and mortality clearly fall with increasing time from MI, but it is not currently possible to give an accurate estimate of risk at a given time point following infarction. American guidelines recommend delaying elective surgery for at least 60 days post-MI where possible to mitigate this risk.[3]

### *Optimisation*

#### Non-invasive Cardiac Stress Testing

- The 2014 European Society of Cardiology/European Society of Anaesthesia (ESC/ESA) and the AHA/ACC guidelines propose preoperative stress testing if all the following criteria are met:
- Surgery is elective.
- Patient has poor functional capacity limited by angina or shortness of breath (4 Metabolic equivalents (METs), or with unknown functional capacity).
- Patient has an elevated perioperative risk of major adverse coronary events.
- Testing will impact decision making for perioperative care.[3,5]

Patients with excellent functional capacity (>10 METs) need not have exercise stress testing. Guidance is less clear regarding those patients with elevated cardiac risk and moderate to good functional capacity (4-10 METs), for whom "...it may be reasonable to forgo further exercise testing...and proceed to surgery."[3]

**Table 2:** Recommended Timing of Elective Noncardiac Surgery Following Percutaneous Coronary Intervention (PCI)[3]

| Type of PCI | Timing of Noncardiac Surgery after PCI |
|---|---|
| Balloon angioplasty | 14 days |
| Bare-metal stent | 30 days |
| Drug-eluting stent | 180 - 365 days |

#### Coronary Revascularisation

Indications for preoperative coronary artery revascularisation in patients at risk of myocardial ischaemia are similar to the indications outside of the perioperative setting.[3,5]

In particular, no benefit has been shown for preoperative prophylactic revascularisation in patients with stable or asymptomatic coronary artery disease.[6] Revascularisation with either PCI or surgery has not been shown to improve outcomes with the caveat that studies invariably excluded patients with a strong indication for cardiac surgery, such as left main stem disease or its equivalent.

## MEDICATION CONSIDERATIONS

#### Beta-Blockers

Existing literature on perioperative use of beta-blockers has been muddied by fraudulent research. Guidelines suggest continuing beta-blockers for those already taking them, and uncertainty exists about starting patients who are at risk of perioperative myocardial ischaemia on beta-blockers de novo.[3,5] Careful titration to heart rate in high-risk patients may be beneficial and physiologically attractive. However, in adopting a one size fits all approach, whilst reducing MI, starting patients on beta-blocker could lead to increased mortality and stroke risk, likely due to drug-induced hypotension.

#### Aspirin

Continuing aspirin perioperatively is contentious subsequent to a recent large randomised controlled trial (RCT) that showed an increased rate of significant bleeding without improved mortality or reduced nonfatal MI.[7] Current consensus guidelines recommend that for patients that are on aspirin the decision to continue aspirin should be based on individual risk of perioperative bleeding relative

**Table 3:** Determinants of Myocardial Oxygen Demand and Supply

| Physiological Goals to Increase Myocardial Oxygen Supply | Physiological Goals to Decrease Myocardial Oxygen Demand |
|---|---|
| Low-normal heart rate | Low-normal heart rate |
| High oxygen content of blood ( $SaO_2$, Hb) | Low myocardial wall tension or afterload (avoid hypertension and excessive fluid administration) |
| High-normal aortic pressure | Avoid increased myocardial contractility |
| Reduced coronary vascular resistance | |
| Reduced coronary vascular resistance | |

to risk of thrombotic complications.[3,5] Separate guidelines exist for those who have had recent acute coronary syndrome (ACS) or PCI.

### Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin-receptor blockers (ARBs)

Controversy exists regarding use of ARBs and ACEis perioperatively. American guidelines suggest it is reasonable to continue their use,3 whereas European guidelines suggest discontinuing therapy if the indication is for hypertension.[5]

### Statins

Statins may reduce the incidence of perioperative MI. Statins should be continued if patients are already on them and could be initiated in patients undergoing vascular surgery at least 2 weeks preoperatively,[5] although there are no large-scale prospective trials to confirm this approach.

### Clonidine

There is no evidence of benefit from prophylactic use of preoperative clonidine.

## Emergency Surgery

Elective surgery allows time for a thorough workup and optimisation of high-risk patients. This benefit is sometimes outweighed by the consequences of delaying emergency surgery. In these circumstances, the AHA/ACC guidelines recommend proceeding using "appropriate monitoring and management strategies based on the clinical assessment."[3]

# INTRAOPERATIVE CONSIDERATIONS

## Physiological Goals

Two main mechanisms are postulated to cause perioperative myocardial ischaemia—acute coronary artery plaque rupture or instability and myocardial oxygen supply-demand imbalances (often in the presence of stable coronary artery disease). The proportional contribution of each mechanism is contentious. Contributing factors include increasing myocardial oxygen demand from sympathetic response to pain, trauma, and inflammation, and reduction in myocardial oxygen supply from anaemia, hypoxia, hypotension, and arterial thrombosis from perioperative hypercoagulability.

It is the myocardial supply-demand imbalance that can be modified intraoperatively to prevent myocardial ischaemia. Myocardial oxygen supply is governed by the oxygen content of blood and coronary blood flow. Blood oxygen content is mainly determined by haemoglobin concentration and $SaO_2$ and coronary blood flow is increased by increasing diastolic time (inversely proportional to heart rate), mean arterial blood pressure and calibre of coronary arteries. The calibre of the coronary arteries is largely controlled by metabolic autoregulation to meet the demands of the myocardium and by the myocardial wall tension. In pathological states, the calibre can be decreased by atherosclerosis.

Myocardial oxygen demand is increased with increasing heart rate, afterload, myocardial wall tension, and myocardial contractility. Although techniques to match myocardial oxygen supply and demand would seem prudent in the patient with ischaemic heart disease, not all have supporting evidence for improved outcomes.

### Oxygen

Emerging evidence from the non-perioperative setting suggests that hyperoxia can increase infarct size in acute ST-elevation MI.[8] in the perioperative setting, a non–statistically significant association between high $FiO_2$ and acute coronary syndrome has been demonstrated.[9] Although further evidence is required, a pragmatic approach would be to maintain normal oxygen saturations, using the lowest possible $FiO_2$.

### Heart Rate

Large doses of prophylactic heart rate–reducing agents given preoperatively have not proved to be beneficial.[10] However, avoiding tachycardia with careful titration of analgesia and beta-blockers makes theoretical sense and has not been sufficiently studied to discredit.

### Transfusion Thresholds

Weak evidence suggests a higher transfusion threshold (such as Hb >100g/dL) might result in better outcome for patients with acute coronary syndrome[11]; however, no survival benefit has been demonstrated in higher transfusion thresholds for those at risk of cardiovascular disease perioperatively.[12] The National Institute for Health and Care Excellence (NICE) guidelines recommend a restrictive transfusion threshold of 70g/L unless the patient has acute coronary syndrome, in which case the more liberal threshold of 80g/L is recommended. Further research is needed to clarify the appropriate transfusion threshold for patients with stable coronary artery disease; however, patients with signs of ischaemia or who are particularly high risk may theoretically warrant a transfusion threshold of 90 or 100g/L.

### Temperature Control

Some studies suggest mild hypothermia is associated with increased perioperative myocardial ischaemia and cardiac events when compared with normothermia. The mechanism for this is not clearly understood.

# ANAESTHETIC TECHNIQUE

There is no strong evidence to support a specific anaesthetic technique in preventing myocardial ischaemia.

### General Anaesthesia vs Regional/Neuraxial

Although some controversy exists, the majority of the evidence would suggest there is no statistically significant difference between general, neuraxial, or regional anaesthetic technique.[13–15] Whether this is because the studies are underpowered or represent a true finding is unclear. A confounding issue is that high-risk patients, such as those who have had a recent MI or PCI, are more likely to be on antiplatelet therapy, which may preclude neuraxial and regional techniques, thus resulting in overrepresentation of high-risk patients in the general anaesthesia groups.

### Nitrous Oxide

The addition of nitrous oxide to a general anaesthetic does not appear to increase mortality at 1 year or cardiovascular complications at 30 days in patients at risk of cardiovascular complications.[16]

### Volatile compared with Total Intravenous Anaesthesia (TIVA)

There is insufficient evidence to recommend TIVA or volatile as a preferred option in the prevention of myocardial ischaemia in noncardiac surgery.

### Cyclooxygenase-2 (COX-2) Inhibitors

There is a view that selective COX-2 enzyme inhibitors result in a prothrombotic state which increases the risk of MI. Two large meta-analyses[17] have supported this view with increased risk of MI for those taking COX-2 inhibitors compared with a placebo.

## INTRAOPERATIVE MONITORING

Each patient will have a given baseline risk of perioperative myocardial ischaemia (as discussed earlier) and monitoring should initially be dictated by this. Specific monitoring options include the following:

### Electrocardiogram (ECG)

ECG monitoring is a standard of care according to the Association of Anaesthetists of Great Britain and Ireland (AAGBI) Recommendations for Standards of Monitoring During Anaesthesia and Recovery. ECG is a cheap, easy, and noninvasive means of monitoring for myocardial ischaemia. The addition of precordial leads to the standard 3-lead ECG for patients at risk of myocardial ischaemia increases its sensitivity. A small intraoperative study indicated that in isolation, leads V5 and V4 were most sensitive (75% and 61+% respectively). Combining leads increases sensitivity, with V4 and V5 having a 90% sensitivity, leads II and V5 having 80% sensitivity, and leads II, V4, and V5 having a sensitivity of 96%.[18] A more recent study showed that 2 or more precordial leads are required to achieve a sensitivity for MI or ischaemia of 95% or more.[19] Automated ST-segment analysis, while not as good at detecting ischaemia, can alert the anaesthetist to ECG changes.

### Blood Pressure Measurement

Intraoperative hypotension has an association with adverse cardiac events.[20] Mean arterial blood pressure is also one of the determinants of myocardial oxygen supply. It would follow that accurate measurement and timely treatment of hypotension (and hypertension) is important in those at risk of myocardial ischaemia. Arterial line placement gives accurate real-time blood pressure measurement to aid these objectives. The potential for adverse consequences of hypotension means that invasive blood pressure monitoring should be considered in high-risk patients.

### Transoesophageal Echocardiography (TOE)

TOE detects myocardial ischaemia by identifying regional wall motion abnormalities. TOE has associated risks and costs, and it requires an experienced operator. For these reasons routine TOE monitoring for those at risk of myocardial ischaemia is not recommended except for in response to persistent intraoperative haemodynamic instability.[3]

### Pulmonary Artery Catheter

Routine use of pulmonary artery catheters in high-risk patients is not recommended.[3,5]

## DIAGNOSIS OF ISCHAEMIA AND INFARCTION

### Acute Myocardial Ischaemia (or Acute Coronary Syndrome)

Myocardial ischaemia is identified by a patient's symptoms and signs or from ECG abnormalities. Symptoms of ischaemia (such as pain in the chest, mandible, or upper extremity) may be absent in the perioperative setting where anaesthesia or strong analgesia has been administered.[21] Other signs of ischaemia include tachycardia, haemodynamic instability, and evidence of pulmonary congestion (such as reduced oxygen saturations, lung compliance, or wheeze). ECG criteria to diagnose acute myocardial ischaemia require at least 2 anatomically contiguous lead with the following[22]:

i. ST elevation at the J point of at least 1mm (depending on location) or
ii. ST depression of at least 0.5mm, and/or T wave inversion of at least 1mm.

### Acute MI

MI is defined as myocardial cell death due to prolonged myocardial ischaemia. It is diagnosed by[22] a rise of cardiac biomarker value above the 99th percentile limit with at least 1 of the following:

i. Symptoms of ischaemia,
ii. New ST-segment T wave changes or new left bundle branch block,
iii. New pathological Q waves,
iv. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
v. Identification of an intracoronary thrombus by angiography or autopsy

OR: Cardiac death with symptoms suggestive of myocardial ischaemia.

It is important to note that the above diagnostic criteria have not been created for the perioperative setting. An elevated troponin after noncardiac surgery, even without other features of ischaemia independently increases the risk of 30-day mortality.[21] With this in mind, a new perioperative diagnosis has been created—myocardial injury after noncardiac surgery (MINS). MINS is diagnosed by a postoperative peak troponin T of 0.03ng/mL or greater due to myocardial ischaemia.[21] Although a diagnosis of MINS has prognostic significance, the clinical utility remains uncertain.

### Management of Myocardial Ischaemia

Once myocardial ischaemia is suspected, management strategies are as follows:

### Confirm Diagnosis

i. Obtain 12-lead ECG.
ii. Consider transoesophageal or transthoracic echocardiogram if haemodynamic instability is detected.
iii. Obtain baseline and 4-hour troponin levels.

### Optimise Myocardial Oxygen Supply-and-Demand Balance

i. Pause surgery if appropriate while the situation is stabilized.

ii. Achieve physiologic goals as mentioned earlier: low/normal heart rate, normal blood pressure, normal oxygen saturations with the least $FiO_2$ possible, avoid hypothermia, avoid excessive fluid.

iii. Administer medications: beta-blockers to achieve low or normal heart rate provided no hypotension, consider giving aspirin (via nasogastric tube if under general anaesthesia), and a glyceryl trinitrate (GTN) infusion.

iv. Consider use of intra-aortic balloon pump, as guided by cardiologists.

### Consider Abandoning Surgery

This will be situation-specific and involve a multidisciplinary discussion. Considerations include the following:

i. How unstable is the patient?

ii. How urgent is the surgery?

iii. Can the surgery stop rapidly if the patient deteriorates?

If the surgery is continued, having an experienced surgeon to ensure shortest surgical time might be of benefit to the patient.

### Consult Cardiologist

If evidence of ST-elevation MI is present on ECG, or there is haemodynamic instability, emergent cardiology opinion is recommended to consider need for PCI. Thrombolysis is usually contraindicated if surgical incision has been made.

## POSTOPERATIVE CONSIDERATIONS

Postoperative management will be patient-specific but considerations include the following:

- Postoperative placement: consider more intensive monitoring as appropriate, including need for telemetry.
- Consider need for serial ECGs or troponins depending on index of suspicion of MI.
- Ensure cardiology follow-up or in-patient review if infarct is suspected.
- Ensure good analgesia, euvolaemia, and the addition of beta-blockers (blood pressure allowing) to minimise tachycardia.
- Maintain normal oxygen saturations with judicious oxygen therapy.
- Commence aspirin and consider PGY12 inhibitor as guided by cardiology opinion.

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Update in
Anaesthesia

Review

# Saddle block

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**Summary**

Saddle block is a spinal anaesthetic restricted to the perineal area, or that part of the body in touch with a saddle. It is achieved by using a small dose of hyperbaric solution of local anaesthetic and maintaining the patient in a seated position after injection. One of the major advantages is avoiding hypotension. It also allows rapid mobilization of the patient for the surgical procedure. Certain surgical procedures have an increased risk of urinary retention when performed under saddle block.

## INTRODUCTION

Spinal anaesthesia was first described more than a century ago and remains a popular technic. While it is difficult to produce a unilateral anaesthesia with successful results,[1,2] saddle block is a spinal anaesthesia located mainly at perineal territory and was described after the Second World War. It was widely used in Anglo-Saxon countries until the 1960s, especially in obstetrics, before being replaced by more flexible epidural anesthesia.[3] Saddle block provides anaesthesia of the perineum, tip of the coccyx, medial and bottom of the buttocks and posteromedial part of the thighs covering an area that for a rider would correspond to that in contact with a saddle. Such anaesthesia is obtained by injecting a small dose of hyperbaric local anaesthetic (LA) in a patient maintained in sitting position for a few minutes to facilitate preferential impregnation of sacred roots (S1 to S5) responsible for innervation of perineum, external genitalia and anus. The saddle block causes a parasympathetic blockade at the bladder level which may result in bladder and rectal atony which is advantageous because of sphincteric relaxation for the operator.

Proctologic surgery (eg hemorrhoid excision, fistulas, sphincterectomies, condyloma excision) is one of main indications of saddle block. The anaesthesia it provides is particularly suitable for this very painful surgery that additionally requires a fully relaxed sphincter. A slightly extended block decreases, as much as possible, the risk of acute retention of urine, a common complication after this surgery.

Opioids should be avoided in combination with LA as they increase the incidence of urinary retention. Indications for the saddle block are noted in Table 1 and it is especially useful in outpatient surgery.

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**Table 1:**

| Procedures for saddle block |
|---|
| Hemorrhoid excision, fistulas, sphincterectomies, condyloma excision |
| Soft tissue surgery at the perianal and gluteal level |
| Pilonidal cyst |
| Localized abscess |
| Coccyx surgery |
| Prostate biopsy |
| Surgery of the urethra |
| Interventional hysteroscopy |
| Obstetric delivery and associated procedures |

### Performance of the Saddle Block

Spinal puncture is performed in a monitored patient in the sitting position. The needle is inserted in the lower lumbar region, i.e. the interspinous space L4-15 or L5-S1. Using a Whitacre® type pencil needle of 25 or 27 Gauge reduces the incidence of headache after puncture of the dura mater. The distal eyelet of this needle needs to be directed downward or caudally. With clear CSF flow, the hyperbaric solution of LA is injected as slowly as possible, without air bubbles, to deliver as much local anaesthetic as possible to sacral territory. To "fix" the block without extension, the patient is kept in a sitting position for at least ten minutes. However, with lower the doses of LA, the patient should remain longer in the sitting position. The baricity of the LA solution and the position of the patient after the injection affect the caudal or cephalic diffusion of anaesthesia[4] so hyperbaric anaesthesia is used to insure a caudad block. When sitting is difficult for a patient due to painful lesions, sedation with low doses of opioids may be useful.

### Solutions and doses of local anaesthetic

Central to the successful saddle block is the use of a hyperbaric solution of LA, i.e. a solution whose density at 37°C is greater than that of CSF. Commonly all solutions with a density greater than 1.013 are considered hyperbaric. In a seated patient, the LA naturally flows in the caudal direction in the CSF, bathing the sacral roots. With the limited cephalic extension, better hemodynamic tolerance of the block is obtained. Otherwise duration of the block is shorter than with an isobaric solution (Table 2).

For 20 years, many studies have implicated lidocaine in the occurrence of root irritation syndrome: transient pain and paresthesia essentially at lumbar level and in lower limbs that is regressive in a few hours or days.[9] The frequency of root irritative syndromes is 8% with 4% mepivacaine compared to 22% with 5% lidocaine. Even with a decreased frequency, mepivacaine, like lidocaine is not recommended for this block. Bupivacaine 0.5% is therefore the anesthetic agent of choice. Ropivacaine is not currently commercially available in hyperbaric solution. It is possible to increase the baricity of the solution by the addition of 10% glucose.

The most commonly used dose in proctology is 4 to 6mg of bupiviacine; this provides a block of one-hour duration.[4] The lower the dose of LA, the shorter the duration of the block. Increasing the dose shortens the onset of the block but lengthens the duration and increases its cephalad extension. Some anaesthetic teams used very low doses of bupivacaine to obtain a very short block limited to perianal area. Wassef et al. compared two groups of 40 patients receiving either 1.5mg or 6mg of bupivacaine. With the dose of 1.5mg, they obtained a quality sensory block without motor block, with a shorter duration (98min vs. 147min), a decreased time to voiding (121min vs. 236min) and a faster discharge (126min vs. 249min).[5]

The potency of ropivacaine is approximately 60% of bupivacaine with a very low incidence (0.1%) of nerve root irritation around. The pharmacological profile of ropivacaine fulfills all the prerequisites for ambulatory surgery. Ropivacaine was compared with lidocaine in outpatient anorectal surgery with an interesting clinical profile.[6] Two other short action LA, articaine and 2-chloroprocaine, are currently used in Anglo-Saxon countries without reports of transient irritation syndrome or neurological lesions. Articaine at a dose of 50-80mg provides 60 minutes anaesthesia with complete resolution at 150 minutes. Two-chloroprocaine at the dose of 40-50mg provides 45 minutes anaesthesia with complete resolution at 103 minutes.[7,8]

### Interest of saddle block

The saddle block is technically simple to perform. The limited duration of the block is adapted to short procedures usually less than an hour and often performed on an outpatient basis. Furthermore, functional recovery from the block is fast. Schmittner et al. compared 201 patients with perianal surgery, in two groups: SB (with 5mg of bupivacaine) to an intravenous general anaesthetic (GA) (Propofol / fentanyl).[10] Time in PACU averaged five minutes (1-45) in the SB group and 44 minutes (4-148) in the GA group. The patients were able to eat more quickly in the SB group, and required less analgesics; 30% vs 58% in GA group. Time to void and mobilization were identical in both groups. In most cases, the patients in the SB group did not have lower limb motor block. Propofol sedation on demand has been proposed to improve the comfort of patients during surgery with SB however, an increase in the incidence of nausea and a longer delay for mobilization and spontaneous urination were noted.[11]

Saddle block induces few hemodynamic changes requiring fluid resuscitation, and in such case, use of a vasoconstrictor is preferred. The risk of urinary retention is related to surgery (proctology), age (> 70 years), urological history, sex (male) and the use of intrathecal morphine.[12]

### Ambulatory surgery

Saddle block is particularly suitable for surgery ambulatory. The duration of PACU stay is very short. The immediate postoperative analgesia it provides can be supplemented by infiltration techniques and the use of parenteral or intravenous analgesics which themselves cause of side effects and may delay home discharge. In proctologic surgery where there is risk of urinary retention regardless of the mode of anaesthetic technique, the patient should be discharged only in case of confirmed voiding.[13]

### Conclusion

Saddle block is appropriate for perineal surgery, procedures on the tip of the coccyx, the medial and inferior portions of the buttocks and the posteromedial aspect of the root of the thighs. It provides excellent relaxation of the anal sphincter and is preferred in proctologic surgery. Due to its simplicity, efficiency and postoperative analgesia, this technique is particularly suited to ambulatory care. There is a risk of urinary retention that can be assessed by use of bladder scan.

**Table 2:**

| **Density and baricity of solutions** | | |
|---|---|---|
| | **Density** | **Baricity** |
| Water | 0,9937 | 0,9931 |
| CSF* | 1,0003 | 1,0000 |
| Isobaric bupivacaine | 0,9993 | 0,9990 |
| Hyperbaric bupivacaine | 1,0210 | 1,0207 |
| *CSF cerebrospinal fluid | | |

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Update in
Anaesthesia

Clinical Article

# The Erector Spinae Plane Block: A Review of Current Evidence

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**Summary**

- From the evidencewe have available, the ESP block should be considered an alternative analgesic option for patients with acute or chornic pain of the trunk
- Most of the favourable data for the ESP block relies on its use as part of a multimodal analgesic package, and this should be considered when planning a patient's care.
- Further research needs to be conducted to determine its true effectiveness compared with other regional techniques as well as optimal dosing regimens.

**KEY POINTS**

- The erector spinae plane block is an easy-to-perform regional anaesthesia technique with a wide range of clinical applications.
- Most of the current research has focused on its use in thoracic and trunk surgery.
- Many experts now consider the erector spinae plane block an alternative analgesic option to thoracic epidural analgesia and paravertebral blocks, especially where these techniques are contraindicated.
- The block has a good safety profile with very few reported complications.

## INTRODUCTION

Interfascial plane blocks are the current hot topic in regional anaesthesia. The 19th-century German surgeon Carl Ludwig Schleich is seen by many as the father of infiltration anaesthesia. His work from 1899 titled "Painless Operations. Local Anaesthesia With Indifferent Liquids" described the use of local anaesthetic (LA) agents to relax the muscles of the anterior abdominal wall and provide analgesia to aid surgery.[1] This was the origin of a procedure that is now practiced worldwide, the rectus sheath block. These techniques have had to bide their time for use in clinical care as their safety, efficacy, and reproducibility have been difficult to assess. However, several factors have led to a seemingly exponential growth in fascial plane block research, description, and utility. The advent of readily available ultrasound technology in modern-day health care and the production of longer-acting amide LAs have had a major impact. A greater driver has probably been the desire, and some would argue necessity, to move away from traditional neuraxial techniques used in the perioperative care of patients undergoing thoracic and abdominal surgery. With surgical techniques becoming less invasive, the introduction of enhanced recovery pathways, and the increased use of anticoagulation therapies, the use of epidural anaesthesia has decreased among many clinical practitioners. In addition, Blanco's 2007 publication of a "no pops" ultrasound-guided transversus abdominus plane (TAP) technique has led researchers to explore various planes for interfascial blocks.[2] Currently, the greatest volume of work produced in this field is focused on truncal interfascial plane blocks, one of which is the erector spinae plane (ESP) block.[3]

This tutorial will look at the current research and evidence in the clinical application of the ESP block. We will explore its inception through to the results of recently published randomised controlled trials and postulate what the future holds for this novel technique. The technique itself will be described in detail in the Anaesthesia Tutorial of the Week article on ESP.

## ESP BLOCK: WHAT IS IT?

The ESP block is a novel interfascial paraspinal plane technique that was initially used by Forero et al[4] for 2 patients with severe chronic thoracic neuropathic pain and 2 patients undergoing video-assisted thoracoscopic surgery. The authors described 2 techniques for this block. One was in a patient with neuropathic pain from metastatic seeding to the ribs,

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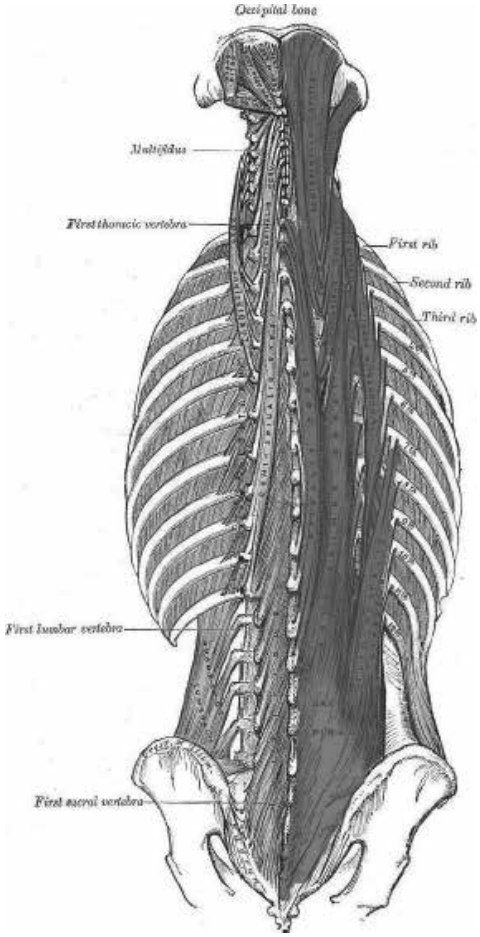


**Figure 1.** Red highlighted structures indicate the 3 columns of the erector spinae muscles. Medial to lateral: spinalis, longissimus, iliocostalis. Source: Henry Vandyke Carter [public domain], image reproduced from *Gray's Anatomy* (figure 389; "Deep Muscles of the Back"). CC BY 3.0.

where they injected LA into the plane between the rhomboid major and erector spinae (ES; ie, superficial to the ES). The patient had complete resolution of pain. In the other 3 cases, LA was deposited deep to the ES, which similarly produced the desired analgesic effect but also provided a cutaneous sensory block.

The standard practice for performing an ESP block today uses ultrasound to deposit LA deep to the 3 columns of ES muscles (iliocostalis, longissimus, spinalis), which run the length of the spine from the base of the skull to the medial crest of the sacrum (Figures 1 and 2). They all have attachments to the transverse processes, the level of which is dependent on the specific muscle. Overlying the ES complex are 2 further layers of muscle: the trapezius and rhomboid major (Figure 2).

## HAS THE ESP BLOCK CAUGHT ON? WHAT DOES THE LITERATURE SAY?

Since Forero's publication in Regional Anesthesia and Pain Medicine in September 2016,[4] there has been wide interest in the ESP block. In the 2 years that followed, there had been close to 100 relevant publications (Figure 3), and based on a literature search conducted in June 2019 via EMBASE, Medline, and PubMed, that number has far been exceeded.

As with any novel regional anaesthesia technique, the initial interest in the block led to an abundance of clinicians attempting to replicate the effects in their own patients. The result was a wealth of case reports with a wide range of clinical applications. Tsui et al[5] recently performed a pooled review of 242 cases relating to the ESP block. After applying inclusion criteria to their search, they found that 90.5% of publications were either case reports or case series, 5.5% were anatomical cadaver studies, and only 2.4% were randomised controlled trials. Most publications originated from Turkey (25%), with Canada and Japan producing the second and third most articles, respectively.

## ANATOMICAL STUDIES AND PROPOSED MECHANISM OF ACTION

As with all fascial plane blocks, the aim of the ESP block is compartmental spread; its efficacy relies on the LA agent passively distributing within the plane to reach target nerves. Absorption and diffusion of LA across tissue planes also appear to play a role in the extent and quality of the block.

The working theory is that because of the discontinuity of the intercostal muscles, LA diffuses anteriorly to the ventral and dorsal rami of the spinal nerves and through the intertransverse connective tissue to enter the thoracic paravertebral space (Figure 4).

### Is the ESP Block a Surrogate for the Paravertebral Block? How Far Does the Injectate Spread?

Further imaging studies have been performed to determine the extent of LA spread as a means of explaining the true mechanism of action. In Forero's publication, the authors expanded on the case series by analysing the spread of injectate both on computerized tomography (CT) imaging and in cadavers.[4] In 1 patient, after 25mL of solution

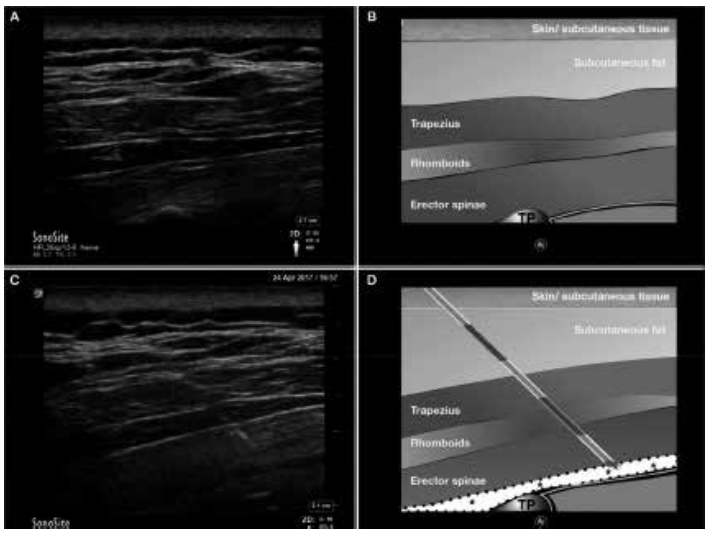


**Figure2.** (A, B) Demonstration of the muscle layers and bony landmarks seen on ultrasound when performing an erector spinae plane block at the thoracic level. Layers from superficial to deep: skin/subcutaneous fat, trapezius, rhomboids, erector spinae, transverse process. (C, D) Needle entry seen through the muscle layers on the vector from the upper left to lower right of the image. Local anaesthetic has been infiltrated deep to the erector spinae (*). The hypoechoic area produced as a result is indicated by the white marked area.

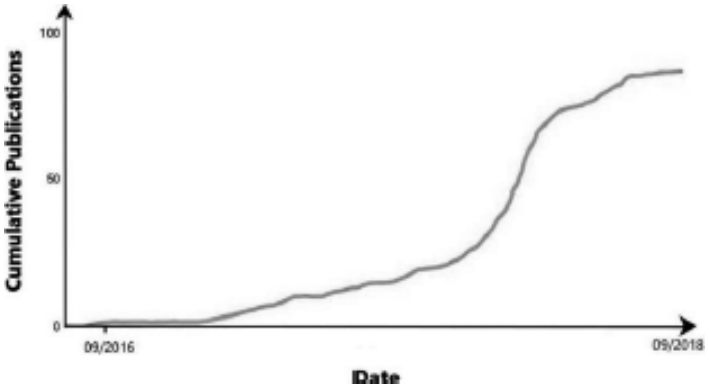


**Figure 3.** Graphical representation of the rapid growth in publications relating to erector spinae plane block.

was injected superficially to the ES muscles, CT imaging revealed cephalocaudad spread from T1 to T11 with minimal lateral spread. In their cadaveric work, they injected methylene blue dye superficial to the ES muscle bilaterally in one cadaver and deep to ES bilaterally in another. Dissection of the former cadaver demonstrated staining of the lateral branches of the spinal root dorsal rami in a longitudinal fashion but no anterior spread beyond the intercostal muscles. With the second cadaver, and injection deep to the ES muscle, the spread of the dye was much greater and included the area deep to the intercostal muscles, through the costotransverse foramina, and close to the spinal nerve root ventral and dorsal rami.

Chin et al6 demonstrated in a cadaveric study that with 20 mL of dye injected at the transverse process of T7 (below the ES muscle), spread was seen cranially up to the lower cranial/upper thoracic vertebrae and caudally as low as the third lumbar vertebra.

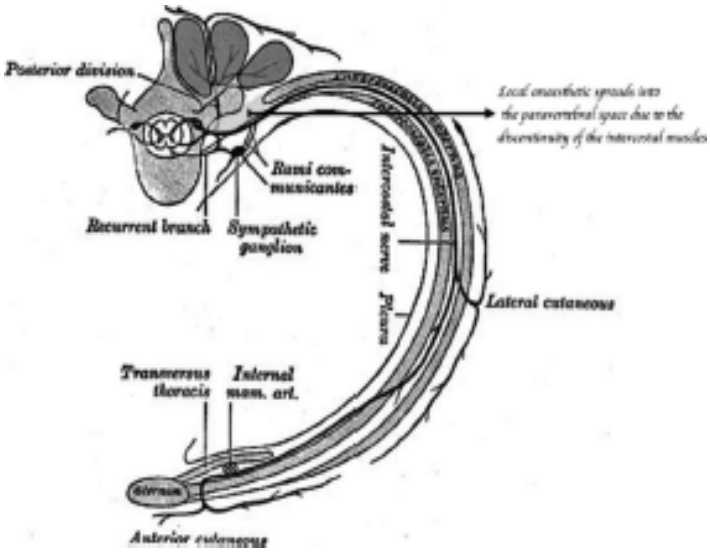


**Figure 4.** Brown highlighted structures indicate erector spinae muscles. The green highlighted area indicates local anaesthetic (LA) deposited below the erector spinae complex. The LA injection spreads into the paravertebral space because of the discontinuity of the intercostal muscles. Source: Henry Vandyke Carter [public domain], image reproduced from *Gray's Anatomy* (figure 819; "Diagram of the Course and Branches of a Typical Intercostal Nerve"). CC BY 3.0.

The cadaveric work by Adhikary et al[7] analysed the spread of radiocontrast dye deep to the ES muscle complex in 3 fresh cadavers. Their results confirmed that seen with Forero et al[4] with craniocaudal spread up to 9 vertebral levels along the paraspinal muscles and in the intercostal space (Figure 5). There was also dye seen in the neural foramina and epidural space.

The case report by Schwartzmann et al[8] of ESP block using gadolinium clearly showed the spread of contrast into the paravertebral space, through the neuroforamina, and a resultant circumferential epidural spread over 7 thoracic levels (Figure 6).

All of these results suggest that the ESP block may be an alternative analgesia option to the paravertebral block (PVB), with some evidence demonstrating injectate diffusing into the paravertebral space to also exert its analgesic effects.

However, not all cadaveric studies have had such extensive spread of dye. Yang et al observed only minimal spread into the paravertebral space, and Ivanusic et al failed to demonstrate any spread into the paravertebral space.[9,10] Ivanusic et al[9] performed an ESP block deep to the ES muscle with 20mL of dye on 10 cadavers (ie, 20 total injections). Like previous studies, there was extensive lateral and craniocaudal spread of dye around the ES complex. But only 1 of the injections led to staining of the ventral rami, and there was no spread anteriorly to the paravertebral space. They did, however, acknowledge the tissue tension limitations of cadaveric studies in replicating the spread of LA in vivo and postulated that the intrathoracic pressure changes present in the living may explain the anterior spread into the paravertebral space.

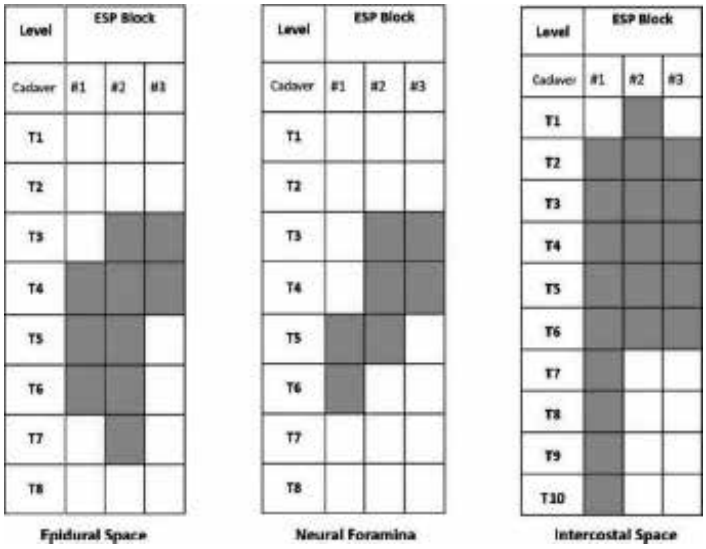


**Figure 5.** Visible craniocaudal spread of methylene blue dye in cadavers after 20-mL injection at the T5 vertebral level. Good spread (range 5-9 vertebral levels) seen in the intercostal spaces. Dye also visualised in the epidural space and neural foramina in all 3 cadavers. Reproduced from Adhikary SD, Bernard S, Lopez H, Chin KJ. Erector spinae plane block versus retrolaminar block: a magnetic resonance imaging and anatomical study. *Reg Anesth Pain Med*. 2018;43(7):756-762, with permission from BMJ Publishing Group Ltd (license 4614451453587).

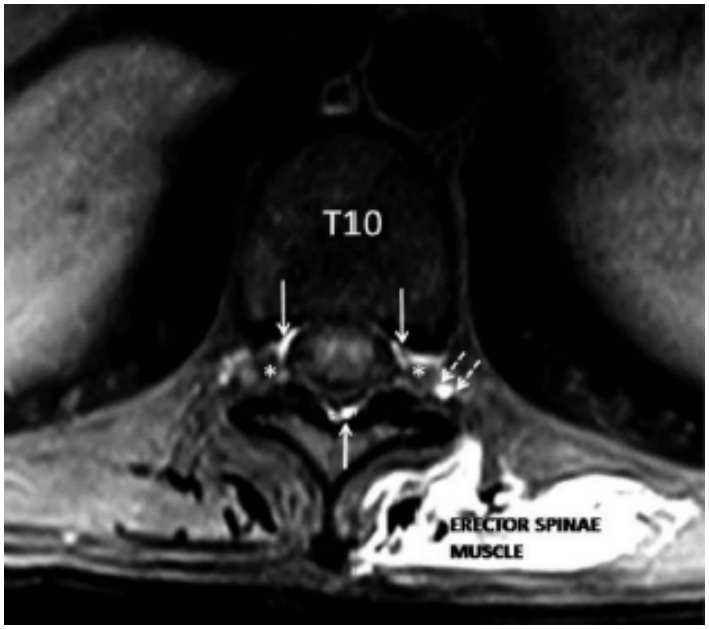


**Figure 6.** Gadolinium magnetic resonance image at 45 minutes after left erector spinae plane block. White arrows: circumferential epidural spread. Dashed arrows: paravertebral spread. Asterisks: bilateral neuroforaminal spread. Reproduced from Schwartzmann A, Peng P, Antunez Maciel M, et al. Bilateral erector spinae plane block (ESPB) epidural spread. Reg Anesth Pain Med. 2019;44:131, with permission from BMJ Publishing Group Ltd (license 4613860141186).

## WHAT DOES THE EVIDENCE SAY? (LARGER STUDIES)

Spread of methylene blue dye and contrast medium in cadavers is informative, but do these anatomical studies translate to a meaningful clinical effect? To best answer this question, we need to identify the larger clinical trials. Again, because of the relative infancy of the ESP block, the literature is limited, but below are the key clinical areas that have produced data from randomised controlled trials. Unsurprisingly, much of this work centres on truncal surgery. From the pooled review by Tsui et al[5] of the published literature, nearly 90% of the ESP blocks were performed in the thoracic, 9% in the lumbar, and, 1% in the cervical region. Eighty percent were single shot-techniques, and 20% were catheter techniques.

### Rib Fractures

Mortality from rib fractures has been reported to be as high as 33%.[11] A dangerous downward spiral results from disruption of respiratory mechanics and pain, culminating in significant morbidity and mortality. For patients with preexisting respiratory comorbidities and/or opioid sensitivity, regional anaesthesia is often life-saving therapy. Thoracic epidural analgesia was long revered as the gold standard for patients with traumatic rib fracture pain, but myofascial plane blocks (eg, serratus anterior, ES) and PVBs have now become alternative options.

A retrospective cohort study at a level 1 trauma centre in Pennsylvania looked at the analgesic outcomes and the effect on respiratory volumes when performing ESP blocks in patients with traumatic rib fractures.[12] For 79 patients, incentive spirometry volumes, 12-hour opioid consumption, and highest numeric rating scale (NRS) static pain scores were recorded at baseline (ie, pre-ESP block) and up to 72 hours post block. All patients received multimodal analgesia prior to block performance. Most (53%) had between 5 and 7 fractured ribs, and 77% of patients received an ESP catheter to allow a continuous LA infusion into the myofascial plane, with the remaining receiving a single-injection technique. The catheters remained sited until the acute pain team deemed the pain could be managed with oral analgesia alone (mean duration, 3.7 days; range, 0.6-9.3 days). Incentive spirometry volumes nearly doubled from baseline during the first 24 hours, with a mean increase of 545 mL. Moreover, this effect was maintained over 72 hours. Maximum NRS pain scores were statistically significantly reduced, and 12-hour opioid consumption was reduced in patients who received a continuous technique (but this did not reach statistical significance). There was no change in mean arterial blood pressure in any of the patients. Those who had a single-injection ESP block showed less convincing results overall. The authors concluded that the ESP block has become the primary regional intervention for rib fracture patients at their institution. They also suggested its benefit in safety profile for patients with contraindications to neuraxial and perineuraxial techniques (ie, anticoagulated patients).

### Thoracic Surgery

Retraction of ribs and incision of chest wall muscles can make thoracic surgery extremely painful in the postoperative period. The impact on respiratory mechanics is the same as those with rib fractures described above, and these patients will experience the same complications if pain is not adequately managed. Again, currently available evidence leads many clinicians to employ a multimodal analgesic approach with the use of thoracic PVB or neuraxial analgesia (thoracic epidural analgesia [TEA] or intrathecal opioid). However, this will not be appropriate management for every patient, and reported failure rates for PVB and TEA are quoted as high as 15%.[13]

To date, 1 randomized study has been published looking at the use of ESP blocks in adults undergoing video-assisted thoracoscopic surgery (VATS). In their randomized controlled trial, Ciftci et al[14] compared opioid consumption and pain scores of single-shot ESP blocks with a control group (no block). The data showed statistically lower opioid consumption (176.66lg 6 88.83lg vs 717.33lg 6 133.98lg) and pain scores in the ESP group. They also found statistically lower rates of nausea and itching in the ESP group (nausea; P ¼ .010). This study suggests that the ESP block is a suitable opioid-sparing block for patients undergoing VATS, but pain scores were measured only up to 24 hours, and there are no studies comparing PVB/TEA with this technique in this patient cohort.

For open thoracic surgery, there are several case reports and case series describing the successful use of ESP catheters for posterolateral thoracotomy analgesia.[15,16]

### Breast Surgery

ESP blocks are showing promise as a regional technique for breast surgery analgesia. Small randomized controlled trials have shown effective analgesia and reduced postoperative opioid consumption when compared with standard care in patients undergoing surgery for breast cancer (including mastectomy).[17,18] However, 1 prospective randomized trial in radical mastectomy surgery showed lower pain scores and postoperative tramadol consumption if a modified

pectoral nerve block was performed rather than an ESP block.[19] Larger comparator studies need to be conducted to assess the true efficacy and benefit for this surgical cohort.

### Cardiac Surgery

Several studies have been performed using ESP blocks for patients undergoing open cardiac surgery. This is a surgical speciality with procedures that require high intraoperative doses of anticoagulant agents, and so regional anaesthesia has traditionally been avoided. Patients undergoing elective cardiac surgery with cardiopulmonary bypass had significantly lower pain scores (up to 12 hours postextubation) if bilateral ESP blocks were performed rather than standard therapy alone with intravenous paracetamol and tramadol.[20] A patient-matched, controlled before-and-after study showed similar results but also found that postoperative adverse events, time to chest drain removal, and time to first mobilization were all significantly lower if ESP blocks were performed.[21] When comparing TEA and bilateral continuous ESP blocks for cardiac surgery, 1 study found comparable pain scores, incentive spirometry, intensive care unit duration, and number of ventilator days.[22]

### Abdominal Surgery

Rectus sheath (RS) catheters have gained huge popularity as an analgesic technique for postoperative midline laparotomy pain. However, this block provides only somatic analgesia to the midline from T6 to T11. For patients who have transverse incisions, stomas, and drains, RS blocks will not provide analgesia. Alternatives that have been explored include TAP blocks and, more recently, quadratus lumborum blocks. A perceived key benefit of the ESP block over other interfascial blocks for abdominal procedures (RS, TAP) is the anterior spread of injectate into the paravertebral and epidural space. This would block not only spinal nerve roots but also rami communicantes transmitting sympathetic fibres, thus leading to relief from visceral pain. This was highlighted in the small case series by Chin et al[23] with significant relief of visceral pain after ESP blocks seen in 3 bariatric patients undergoing laparoscopic abdominal surgery.

The literature points to a wide spectrum of indications for ESP blocks when considering abdominal procedures. These include laparotomy, nephrectomy (laparoscopic and open), renal transplant, radical prostatectomy, percutaneous nephrolithotripsy, herniorrhaphy, gastric bypass, gastrectomy, and caesarean delivery, to name a few.

Tulgar et al[24] performed a double-blinded, randomized, controlled, prospective study comparing ESP and subcostal TAP blocks in laparoscopic cholecystectomy surgery performed at a tertiary university hospital in Turkey. Sixty patients were recruited and randomized into 3 equal groups: bilateral subcostal TAP, bilateral ESP, and control. All patients received standard multimodal analgesia and an intraoperative remifentanil infusion, and those who received a block had this performed at the end of surgery. A standard mix of 40mL LA was used for all patients. No patients received LA at the surgical site. Tulgar et al[24] found that patients in the 2 block groups had significantly lower rest and dynamic pain scores in the first 3 postoperative hours (P.001) and a lower overall 24-hour analgesic requirement.

Another randomized controlled study, in Egypt, assessed the efficacy of the ESP block for postoperative analgesia in total abdominal hysterectomy.[25] The authors demonstrated that the patients who had blocks had significantly lower fentanyl consumption in the first 24 postoperative hours and significantly lower pain scores in the first 12 hours.

### Lower Limb Surgery

A randomized, controlled, double-blind study looked at the analgesic efficacy of lumbar ESP blocks used for patients undergoing hip and femur surgery.[26] When compared with standard intravenous analgesia, the authors found that the patients with ESP blocks had significantly lower pain scores within the first 6 hours and lower total 24-hour tramadol consumption (control ¼ 226mg 6 35.89mg, ESP block ¼ 130mg 6 50.99mg; P , .001). ESP block was also compared with quadratus lumborum blocks, and both showed similar results overall. The data produced suggest that lumbar ESP blocks may provide effective analgesia for hip and femur surgery as part of a multimodal analgesic strategy.

Given the potential spread of LA into the epidural space, it is feasible that lumbar approaches to the ESP block lead to lower limb weakness. Selvi and Tulgar[27] published a case report describing transient bilateral lower limb weakness after a T11 ESP block.

### Novel Uses

There is an abundance of case reports and small case series in the literature with positive outcomes. Clinicians have investigated the effectiveness of the ESP block on patients undergoing surgery on the upper limbs and spine.[28]

**Table 1.** Weight-Based Local Anaesthetic Concentration and Volume Guide for Erector Spinae Plane Block in Rib Fractures

| | Weight-Based Dosing | | |
|---|---|---|---|
| **Drug** | **50-kg Patient** | **70-kg Patient** | **100þ-kg Patient** |
| *Unilateral* | | | |
| 0.25% bupivacaine, mL | 30 | 40 | 40 |
| 0.5% bupivacaine, mL | 20 (max dose) | 20 | 30 |
| *Bilateral* | | | |
| 0.25% bupivacaine, mL | 20 per side (40 total) | 25 per side (50 total) | 30 per side (60 total) |
| 0.5% bupivacaine, mL | Not advised, not enough volume | Not advised, not enough volume | Not advised, not enough volume |

There is even a case report suggesting the effectiveness of the technique for a refractory tension headache.[29]

Several articles have suggested the ESP block may be used for chronic shoulder pain and surgery on the upper arm.[30]

## CLINICAL QUESTIONS

There remain several clinical questions that require further research.

### What Are the Optimal Volume and Concentration of LA?

- Fascial plane blocks rely on a high-volume, low-concentration technique for optimal efficacy.
- In a mini review, De Cassai and Tonetti[31] determined that 3.6 mL of an LA agent per desired vertebral level spread was adequate in ESP blocks. However, at present, there are no data relating this volume to duration of action.
- Luftig et al[32] specifically looked at the volume and concentration used in 16 ESP block articles (49 cases) when indicated for rib fracture analgesia, to determine optimal regimes. Based on the findings, they created a weight-based guide for ESP block in these patients (Table 1).

### Single Level Versus Multilevel

- As shown, cadaveric and anatomical studies show extensive spread of injectate around the ES complex with varied degrees of spread into the neural foramina and epidural space. Further studies will need to clarify the decision to perform the block at 2 levels if a noncatheter technique is being employed.
- Tulgar et al[33] demonstrated lower postoperative pain scores and opioid use in thoracotomy patients if 2-level ESP blocks were performed rather than single-level blocks.
- Multiple published case reports also describe the successful use of a bilevel approach.[34,35]
- There have been no studies to date directly comparing the clinical efficacy of single-level with multilevel injections/catheters.
- Multilevel injections/catheter insertions may have a role when extensive analgesia of the trunk is desired.

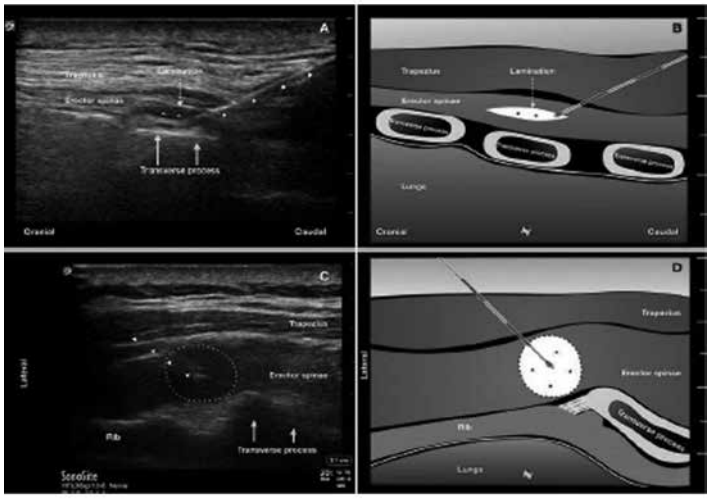


**Figure 6.** T5 vertebral level parasagittal (A, B) and transverse (C, D) approach to the erector spinae plane block. Needle trajectory indicated by arrow heads. In images A and B, the needle tip is located between the muscle fibers, which run parallel to the ultrasound beam in the parasagittal probe orientation. When fluid is injected here (*), the ultrasound appearance may replicate that seen with an interfascial injection (also known as lamination), but the result will be an intramuscular injection. With a transverse approach, as shown in images C and D, the needle tip is similarly placed intramuscularly. However, injection in this orientation results in localised circumferential spread of fluid (dotted circle), which is less likely to be confused with interfascial spread. Reproduced from Narayanan M, Venkataraju A. Transverse approach to the erector spinae block: is there more? *Reg Anesth Pain Med*. 2019;44:529-530, with permission from BMJ Publishing Group Ltd (license 4615000311499).

### What Is the Optimal Approach?

The classically described approach to the ESP block is a parasagittal ultrasound probe position with in-plane needling. Some clinicians report an out-of-plane technique with the same probe position.

- A documented problem with the parasagittal approach is "lamination"—injection between the muscle fibers producing an ultrasound image consistent with spread within the fascial plane (Figure 7).[36] This occurs because of the longitudinal orientation of the muscle fibers in the ES complex.
- The authors observed this phenomenon to occur more frequently when needling for catheter insertion with 16-gauge Tuohy needles.
- With a transverse approach, lamination will not be seen after intramuscular injection.
- The authors of this article recommend first performing a single-shot ESP block with the transverse approach to create a target space for catheter insertion. The catheter can then be sited using a parasagittal or transverse approach. Block success and correct catheter placement rates may be higher with this technique.

### Caveats

- Publication bias: When the outcome of cases and clinical trials is not in favour of an intervention, they may not be submitted for consideration of publication. This means for a new technique such as the ESP block, the already relatively small pool of evidence may suffer from reporting biases.
- As the technique remains in its infancy with most data coming from case reports, there is currently no consensus on dosing regimes for various indications. This makes comparison between studies more difficult.

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Update in
Anaesthesia

# Tranexamic Acid

Originally published as Anaesthesia Tutorial of the Week

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**Summary**

Tranexamic acid significantly reduces peri-operative blood loss in a wide variety of surgical specialties and improves survival in haemorrhage from trauma and birth. In cardiac patients it carries a risk of seizures, especially with higher doses, and theoretically may predispose to thromboembolic disease but clinically relatively few side effects are observed. It is highly cost-effective and requires minimal training to administer. As such the World Health Organisation now include it on the essential medicines list. Future research to clarify dosing regimens, especially in the cardiac and paediatric populations, as well as usage in other surgical disciplines and intracranial haemorrhage is expected.

**KEY POINTS**

- Tranexamic acid reduces bleeding and reduces the need for blood transfusion. It is used in the management of major trauma, haemorrhage, and as prophylaxis in surgery.
- Standard dose is 1g intravenously, over a minimum of 10 minutes.
- The main mechanism of action is anti-fibrinolytic activity. It also possesses anti-inflammatory effects and may help attenuate the systemic inflammatory response syndrome in cardiac patients.
- There has been no evidence of thrombotic events with tranexamic acid use, but theoretical concerns remain, and caution is advised in patients with recent or significant history of venous thromboembolism.
- In cardiac patients it has been shown to increase the risk of seizures, and manufacturers advise against using in any patient with a history of seizures.

## INTRODUCTION

Tranexamic acid was introduced in the 1960s, it reduces bleeding by competitively inhibiting fibrinolysis. It was initially prescribed for heavy menstrual bleeding but is now recommended in a variety of elective surgical procedures to reduce blood loss, and also for the treatment of major haemorrhage. It has relatively few contraindications, is well-tolerated and cheap to use. As such, its use continues to expand into other specialties and surgeries.

The CRASH2 trial (2010) is the largest study to date on tranexamic acid demonstrating a significant (1.5%) mortality benefit when 1g of intravenous tranexamic acid, compared to placebo, was given within 3 hours of injury to trauma patients with suspected major haemorrhage.[1] In the WOMAN trial (2017) 1g of intravenous tranexamic acid was given for the treatment of post-partum haemorrhage resulting in reduced deaths due to bleeding (0.4%), with a greater survival benefit when tranexamic acid is given as close as possible to the onset of post-partum haemorrhage.[2]

The ATACAS trial (2018) studied the effect of tranexamic acid in cardiac surgery and, consistent with the effect seen in other surgical specialties, blood loss was reduced. Relatively high doses (50-100mg/kg) were administered and post-operative seizure rate was increased with tranexamic acid compared to placebo.[3] Some evidence links higher doses with larger reductions in peri-operative blood loss but at the expense of increased seizure rate. Tranexamic acid is also commonly used in orthopaedic surgeries as a 1g prophylactic pre-incision dose in total knee and total hip arthroplasty.[4] Research into its benefits in spinal surgery, intra-cranial haemorrhage, liver resection and paediatrics is ongoing.

After reviewing the pharmacology, contraindications and side effects, this article will consider the use of tranexamic acid in clinical practice across various specialties.

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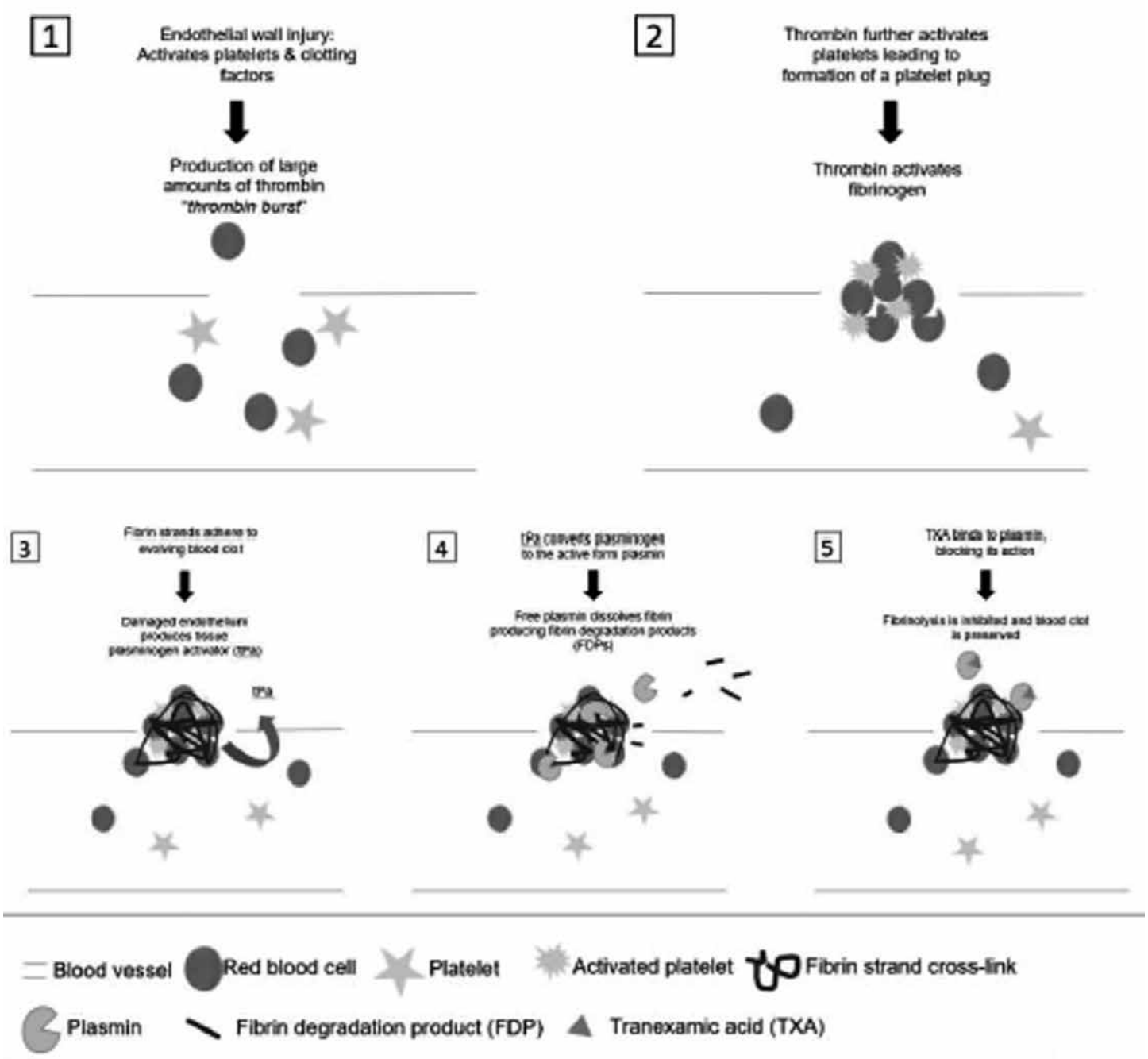
**Figure 1:** The clotting and fibrinolytic systems




## FIBRINOLYSIS AND MECHANISM OF ACTION OF TRANEXAMIC ACID

Tranexamic acid has beneficial actions on fibrinolysis, platelet function and the systemic inflammatory syndrome.[5]

Following trauma, surgery, or exposure to extracorporeal circulations the body's ability to regulate local fibrinolysis is exceeded and generalised fibrinolysis can occur leading to a coagulopathy. Vascular endothelial wall stress activates the clotting cascade leading to platelet activation and plug formation, large amounts of thrombin production and later fibrin cross-links that strengthen the developing blood clot (a mass of red blood cells, white blood cells, platelets, fibrinogen, fibrin and plasminogen). To prevent uncontrolled growth of the blood clot, fibrinolysis is also initiated. Fibrinolysis is activated locally by plasminogen-activators found in endovascular endothelium as well as being produced by macrophages that convert plasminogen to plasmin and promote fibrinolysis at the site of clot formation.[5]

**Table 1:** Dose Adjustment in Renal Impairment

| Serum Creatinine (Imol/l) | eGFR (ml/min) | Dose (IV) | Frequency of Administration |
|---|---|---|---|
| 120-249 | 20-50 | 10mg/kg | 12 hourly |
| 250-500 | 10-20 | 10mg/kg | 24 hourly |
| >500 | <10 | 5mg/kg | 24 hourly |

Tranexamic acid is a synthetic derivative of the amino acid lysine and inhibits fibrinolysis by reversibly binding to lysine-binding sites on plasminogen, thereby preventing the cleavage of fibrin.[5,6] (See Figure 1)

Plasmin acts on platelets to reduce platelet aggregation and adhesion and therefore tranexamic acid, by reducing the formation of plasmin, helps to preserve platelet function.[5] Plasmin and plasminogen also demonstrate pro-inflammatory effects including monocyte activation and cytokine production and whilst the role of tranexamic acid in reducing inflammation is not fully elucidated the expression of several pro-inflammatory genes is altered in the cardiac setting following the administration of tranexamic acid and it demonstrates a reduction in the systemic-inflammatory-response-syndrome and subsequent vasopressor use.[7] It has also been shown to inhibit complement.[6]

There is limited evidence that some patients experience a fibrinolytic shutdown scenario whereby they increase their own plasminogen-activator inhibitor activity and thus would not benefit from tranexamic acid and may become pro-thrombotic if tranexamic acid is given to this subset of patients. This is an ongoing area of research and currently has not impacted clinical guidance on usage.[7]

## PHARMACOKINETICS

### *Absorption*

Maximum plasma concentrations of tranexamic acid are attained within 3 hours of an oral dose and absorption is not slowed by a full stomach. Peak concentrations occur rapidly after intravenous injection and fall in a multi-exponential manner.[6]

### *Distribution*

Tranexamic acid has a volume of distribution of 9-12L and is 3% plasma-protein bound. It has good penetration of joint fluid and synovial membranes as well as crossing the placenta and blood-brain barrier. In both cerebrospinal fluid and aqueous humour, concentrations are 1/10 that of plasma and with minimal concentrations in breast milk (1/100), it is considered safe in breast feeding.[6]

### *Metabolism and Elimination*

Tranexamic acid is excreted unchanged in the urine and 90% is excreted within the first 24 hours after an intravenous dose.[6] Doses should be adjusted in renal insufficiency.

### Routes of Administration, Storage and Compatibility

Oral, topical and intravenous formulations exist but intra-cerebral and intrathecal use are contraindicated due to seizure activity in animals. It has a long shelf-life of 3 years and can be stored at room temperature. Intravenous tranexamic acid is compatible with electrolyte, glucose and amino acid solutions as well as with heparin.[6] (See Table 1)

## SIDE EFFECT PROFILE

### Seizures

Administration of topical tranexamic acid directly to the central nervous system in animals provokes seizures. Clinically, tranexamic acid has been shown to increase the risk of seizures in patients undergoing cardiac surgery, largely when moderate and high doses (more than 10mg/kg) are used. Possible causal mechanisms include inhibition of GABA-A and glycine inhibitory receptors leading to stimulation of excitatory pathways, as well as an increased susceptibility of cardiac patients to post-operative seizures due to emboli introduced during surgery.[3] Increased risk of seizures has not been observed in other clinical settings. However, manufacturers advise avoidance of tranexamic acid in all patients with a history of convulsions.[6]

### Thrombo-embolism

There is a theoretical basis for concerns that tranexamic acid could promote thrombus formation, and this is supported by in vivo

**Table 2:** Side effects of tranexamic acid

| | Side effect | Frequency |
|---|---|---|
| Gastrointestinal | Diarrhoea, vomiting, nausea | Common |
| Central nervous system | Seizures | Unknown |
| | | Associated with high doses |
| Cardiovascular system | Hypotension (fast injection), malaise, VTE | Unknown |
| Immune system | Hypersensitivity | Unknown |
| Eye disorders | Visual disturbance | Unknown |
| Skin | Dermatitis | Uncommon |

animal studies showing a dose-dependent increase in thrombus and risk of thrombo-embolism.[7] However, multiple meta-analyses have failed to show an increased risk of myocardial infarction, stroke, pulmonary embolism or deep vein thrombosis with tranexamic acid compared to placebo.[5,7,8] Subsequently, it is recommended that an acute venous thromboembolism is an absolute contraindication to tranexamic acid, and a risk/benefit analysis must be undertaken if there is a personal history of VTE.[6] (See Table 2)

## CLINICAL USES

Tranexamic acid reduces blood loss in patients with both normal fibrinolysis and hyperfibrinolysis.[6] Hyperfibrinolysis can occur following surgery, trauma, tissue damage or exposure to extracorporeal circulations where the body's natural ability to regulate local fibrinolysis is exceeded and fibrinolysis becomes systemic, leading to coagulopathy. Additionally, during clot formation fibrinogen is consumed rapidly and early tranexamic acid preserves fibrinogen stores during haemorrhage. Therefore, clinicians should aim to prevent, rather than treat, coagulopathy and administer tranexamic acid as early as possible.

It is a cost-effective intervention for preventing bleeding during major surgery across a broad spectrum of surgical procedures, reducing average peri-operative blood loss, and subsequent transfusion, by 34% and 39% respectively.[9] Blood transfusion is costly and scarce, especially in areas with limited resources and poses multiple risks to patients including transfusion-related reactions, immunomodulation and transfusion transmitted infection. (See Table 3)

### Trauma

Trauma is a major contributor to death worldwide with haemorrhage causative in 1/3 of in-hospital trauma deaths. Early clotting abnormalities, including hyperfibrinolysis, occur frequently in trauma patients and substantially contribute to mortality. A large study found that 1g of intravenous tranexamic acid, compared to placebo, reduced risk of death from bleeding by 15% with no increased risk of any adverse events.[1] However, treatment benefit decreases by 10% for every 15 minute delay after the first hour following onset of haemorrhage and therefore should be given as soon as possible but certainly within 3 hours. After 3 hours it should be omitted unless there is clear evidence of hyperfibrinolysis on blood results10.

### Obstetrics

Postpartum haemorrhage is the leading cause of maternal mortality worldwide. Within 1 hour of birth the concentration of plasminogen doubles leading to activation of fibrinolysis. Despite not showing a reduction in the volume of blood loss or transfusion rate, the WOMAN trial demonstrated that intravenous tranexamic acid, compared to placebo, reduced the risk of death from bleeding by almost 1/3 with no increase in adverse events for mother or baby.[2] It should therefore be given as a 1g intravenous bolus as close as possible to bleeding onset (birth) and a further 1g intravenous dose can be repeated 30 minutes later if bleeding continues. It is not to be given if more than 3 hours has elapsed since birth due to lack of treatment benefit.

**Table 3.** Summary Dosing Table

| | Loading Dose (No Faster than 100mg/minute) | Maintenance Dose | Other Considerations |
|---|---|---|---|
| Trauma | 1g IV | 1g IV over 8 hours | Continue 1g 8 hourly if bleeding ongoing |
| Post-partum haemorrhage | 1g IV | 1g IV bolus 30 minutes after initial dose, if bleeding continues | |
| Cardiac | 1g or 5-10mg/kg IV | 1-5mg/kg/hour | |
| Orthopaedic | 1g IV pre-incision | | Consider further 1g IV bolus if ongoing bleeding or blood loss 500mls |
| Spinal | 1g or 10mg/kg IV pre-incision | | |
| All other types of surgery (with risk of >500mls peri-operative blood loss) | 1g or 10mg/kg IV pre-incision | | |
| | 1g or 10mg/kg IV pre-incision | | |
| Haemophilia (both haemorrhage and following minor surgery, dental extraction) | 1g orally 8 hourly for several days prior to procedure | | |
| Hereditary angioedema | 1-1.5g orally 8 hourly | Continue 1-1.5g orally 8 hourly for 2-5 days following procedure | |
| | prophylactically several days prior to planned procedures | | |

### Cardiac

Tranexamic acid has several beneficial actions in patients undergoing cardiac surgery. These patients are at high risk of blood loss, and subsequent transfusion, due to the highly invasive nature of cardiac surgery, high dose anticoagulation and blood lost within the extracorporeal cardiopulmonary bypass circuit. Exposure to the extracorporeal circuit activates the fibrinolytic system and causes platelet dysfunction, thus in addition to its' antifibrinolytic activity tranexamic acid helps preserve platelet function during cardiopulmonary bypass.[3] Patients undergoing major cardiac surgery often suffer a profound systemic inflammatory response syndrome leading to shock and multiorgan failure and tranexamic acid has been shown to alter the expression of several inflammatory genes, dampening this inflammatory response.[5]

Tranexamic acid reduces the rate of blood loss, risk of reoperation due to haemorrhage (which carries increased morbidity and mortality) and the need for blood transfusion with no increased risk of death or thrombotic complications in patients undergoing on-pump or off-pump surgery.[3] However, it does cause an increased risk of seizures demonstrating a dose-dependent relationship. Therefore lower dose tranexamic acid (5-10mg/kg) is being increasingly used in UK cardiac centres with less post-operative seizures observed as a result. Seizures generally occur within hours of surgery and are grand-mal in nature. Those who have post-operative seizures are subsequently more at risk of stroke or death. The risk of seizures is particularly high in the elderly, those with pre-existing renal failure and those undergoing open-heart surgery.[3]

### Orthopaedic

Prosthetic implantation and use of a tourniquet activates fibrinolysis and haemorrhage is common post arthroplasty. Patients presenting for hip and knee joint replacement are often elderly with multiple co-morbidities such as anaemia and ischaemic heart disease, that render them more susceptible to bleeding-related morbidity and mortality. Tranexamic acid significantly reduces blood loss in total hip and knee replacement. Intravenous delivery appears to provide the most benefit but both oral and combination topical/intravenous preparations are favourable to placebo.[4] Tranexamic acid has excellent joint penetration and its use has been fully embedded in total knee and hip arthroplasty fast track protocols in many centres. Similar usage is expected in the future in all types of major arthroplasty.

### Intra-cranial Haemorrhage

In spontaneous haemorrhage tranexamic acid can reduce haematoma expansion and leads to fewer deaths at 7 days with no increased risk of seizures or other adverse events but with no significant improvement in neurological or mortality outcomes at 90 days.[11] Therefore it is not currently recommended in clinical practice but results are anticipated from an ongoing study (STOP-AUST) into the benefit of tranexamic acid in a subset of these patients and a meta-analysis of ongoing multiple smaller trials is planned.

### Spinal Surgery

Research in spinal surgery and tranexamic acid has largely been on smaller studies showing a slight reduction in blood loss and transfusion rate following administration of tranexamic acid but differences have not yet shown to be statistically significant. As there have been no adverse outcomes alongside increasing evidence in most other surgical specialties tranexamic acid is recommended in all spinal surgery that carries a risk of major bleeding (>30% total estimated blood volume) and/or surgery involving fusion at 3 vertebral levels.[12]

### Other Uses

Tranexamic acid has been introduced prophylactically across a wide range of other conditions and procedures including haemophiliacs undergoing any surgery, hereditary angioedema, and prostatectomy. It should be used, unless contraindicated, in any other major surgery at risk of more than 500ml blood loss or loss of 10% circulating blood volume. It is also recommended for treatment of major bleeding from haemoptysis and gastrointestinal haemorrhage.[7,8] Currently a large multicentre trial (HeLiX) is investigating the impact of tranexamic acid on perioperative blood transfusion in patients undergoing liver resection.[13]

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Case Report

# Intrathecal tranexamic acid during spinal anaesthesia for caesarean deliver

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**Summary**

The National Committee on Confidential Enquiries into Maternal Deaths recently received notification of a death in South Africa caused by inadvertent intrathecal administration of tranexamic acid (TXA). TXA is increasingly used during caesarean delivery following updated recommendations from the World Health Organization in 2017. However, its greater availability has led to an international rise in drug errors during obstetric spinal anaesthesia. This case highlights a growing clinical risk, of which all operating theatre staff should be aware. Review of existing operating theatre drug handling practices is required in order to decrease this risk. Recommendations are made that aim to minimise drug errors associated with the use of this potentially life-saving intervention.

## INTRODUCTION

The National Committee on Confidential Enquiries into Maternal Deaths recently received notification of a death in South Africa (SA) caused by inadvertent intrathecal administration of tranexamic acid (TXA). This case highlights a growing clinical risk, of which all operating theatre staff should be aware. Review of existing operating theatre drug handling practices is required in order to minimise this risk.

TXA is included in the World Health Organization (WHO) essential medicines list (EML)[1] as well as the SA National Department of Health EML.[2] It is a synthetic lysine analogue that acts to reduce fibrinolysis through competitive inhibition of plasminogen binding sites. TXA is increasingly being used in the perioperative setting as a result of recently updated WHO guidelines recommending early use of intravenous TXA during caesarean delivery (CD) when excessive bleeding occurs.[3] The key messages from this guideline are summarised in Table 1. This change in practice is largely due to the results of the WOMAN trial, a landmark multicentre study including 20,000 patients that showed reduced maternal mortality due to bleeding with the early administration of TXA in the setting of postpartum haemorrhage.[4] The WOMAN trial showed that if TXA was given intravenously within 3 hours of bleeding following normal vaginal delivery or CD, maternal mortality was reduced by 31%, although the absolute reduction was small (1.7 - 1.2%, risk ratio 0.69, 95% confidence interval 0.52 - 0.91; p=0.008). These benefits were most pronounced in low- and middle-income settings such as SA.[4] The WHO states that 'regardless of the level of health system resources, TXA should be recognized as a lifesaving intervention and be made readily available for the management of postpartum haemorrhage in settings where emergency obstetric care is provided'.[3]

## SA TXA RECOMMENDATIONS

It has been suggested that the high number of deaths due to obstetric haemorrhage (OH) at or after CD in SA is a national emergency,[5] and despite a recent downward trend, OH remains the third most common cause of maternal mortality at ~17%.[6] Accordingly, the nationally endorsed training programme for obstetric emergencies (Essential Steps in the Management of Obstetric Emergencies: ESMOE)[7] has been revised to recommend early intravenous administration of 1g TXA for bleeding during or after CD. Excessive bleeding is now defined as >500mL in the suction bottle, or a decrease in blood pressure accompanied by a rise in heart rate associated with bleeding, as detected by the anaesthetist. This is earlier than the traditional description of at least 1,000mL blood loss during CD, and TXA is therefore being used with greater frequency. While there may be a role for the administration of TXA before CD,[8,9] there is not yet enough evidence from high-quality research to recommend such prophylaxis at a national level.[10] In particular, there is no evidence that prophylactic TXA before CD reduces maternal death.

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**Table 1:** Key messages adapted from the updated World Health Organization recommendations on TXA for the treatment of postpartum haemorrhage[3]

| |
|---|
| Bleeding during CD is defined as a clinical estimate of blood loss >1 000 mL, or blood loss sufficient to cause haemodynamic instability |
| Early use of TXA (within 3 hours of birth), in addition to standard care, is recommended. The use of TXA >3 hours after birth is not supported |
| Administer TXA 1g IV over 10 minutes, with a repeat dose if bleeding continues after 30 minutes, or if bleeding restarts within 24 hours of the first dose. Only IV use is currently supported |
| TXA should be given in all cases of postpartum haemorrhage, regardless of cause |
| TXA should not be given when a clear contraindication exists, such as thromboembolic disease during pregnancy. |

TXA = tranexamic acid; CD = caesarean delivery; IV = intravenous

With increased availability and use of TXA during and immediately following CD, the risk of drug error increases. Our case of maternal death was assessed by independent experts to be due to intrathecal TXA, and occurred in the context of a disturbing international trend. A recent review in Anaesthesia[11] highlighted 21 such cases between 1988 and 2018, 10 of which were fatal. Twenty were due to 'ampoule error'. An accompanying editorial[12] entitled 'Spinal tranexamic acid – a new killer in town' highlighted the dramatic increase in the number of cases since 2009. Seven cases involved CD, 6 of which resulted in death: it appears that mortality is higher following CD than following other surgery. The authors mention anecdotal reports of further cases that have not been formally reported, making the true incidence hard to estimate. Clinicians are understandably reluctant to submit case reports relating to serious medical error. Additionally, cases such as ours that come to light through a confidential enquiry process cannot be published in detail owing to requirements to maintain anonymity. The incidence is therefore probably far higher than currently reported.

## CONSEQUENCES OF INTRATHECAL TXA ADMINISTRATION

Intrathecal TXA is a potent neurotoxin and neurological sequelae dominate the clinical presentation, usually with refractory seizures. Massive sympathetic stimulation frequently occurs, often leading to lethal cardiac arrhythmias such as ventricular fibrillation. Treatment is mainly supportive and should occur in an intensive care setting, including antiepileptics such as diazepam, thiopentone and magnesium sulphate[13] and appropriate antiarrhythmic medication. Early cerebrospinal fluid (CSF) lavage is also recommended, following success in the management of similar cases.[11,14,15] CSF lavage consists of removing 10mL of CSF and replacing this with 10 mL of saline, repeated up to four times.[14,15] The increased mortality rate in the obstetric population following intrathecal TXA is possibly due to decreased CSF volume in pregnancy, leading to increased drug concentrations.[11]

Given the consequences of inadvertent intrathecal TXA administration, is the increased risk justifiable? TXA has become an integral part of the management of OH: the WOMAN trial[4] suggested that a maternal life could be saved with every 267 usages following OH. The potential 'number needed to harm' is difficult to estimate: Palanisamy and Kinsella[12] estimate the risk due to drug error to be <1 in 10,000 spinal anaesthetics, although this is necessarily based on a large degree of conjecture. In Africa, the incidence of severe bleeding during or after CD is almost 6%, while 70% of all complications and 25% of all deaths are secondary to bleeding complications.[16] With a lower recommended threshold for the use of TXA, it is likely that the drug will be given in >6% of cases. The benefits clearly outweigh the risks: the focus therefore needs to be on minimising or eliminating drug error.

## MINIMISING THE RISK OF INTRATHECAL DRUG ERROR

The incidence of perioperative drug errors ranges from one in 133 anaesthetics in retrospective studies[17] to one in two operations in prospective studies (one in 20 drug administrations).[18] Obstetric neuraxial drug administration errors in particular may result in devastating consequences.[19] There is a lack of randomised controlled trials that examine specific techniques and their ability to reduce drug error; recommendations are therefore based on expert opinion and best available evidence.[20,21]

All health facilities should ensure that they have clearly written policies that minimise medication errors, and then audit and appraise errors that do occur.[22] This approach should nurture a culture of drug safety, including multidisciplinary involvement, ongoing education and specific evidence-based interventions.[22] However, despite vociferous calls for changes in practice, merely exhorting doctors to be more careful is often inadequate.[23] Ideally, system changes should make it impossible for error to occur. A similar problem has been encountered with epidural anaesthesia, where the use of Luer universal connectors has allowed for cross-connectivity, resulting in drug errors. This problem is easily preventable with the use of non-Luer connectors, although uptake has been slow.[23] Non-Luer connectors will not prevent a single-shot spinal anaesthesia drug error, however, as occurs with TXA.

The risk of accidental use of the wrong drug increases when ampoules look similar, or are physically available in close proximity.[24] There are now a large number of generic versions of TXA, and changes in supplier and the appearance of ampoules are increasingly common. Human error is to some degree unavoidable, and rather than attempting to eliminate all mistakes, strategies should aim to reduce predictable errors. Solutions that minimise the possibility of human error should be given highest priority.[24] Technology-assisted drug identification, using barcode readers, is one such intervention, although it is unlikely to be immediately available in SA facilities. Pre-filled syringes may be another, although this may be problematic for manufacturers, as each drug must be tested for stability in a pre-filled syringe. Other solutions include the careful reading and labelling of syringes, and a second person or device checking the drug.[19] More costly methods, such as commercially prepared spinal anaesthesia

**Table 2:** Recommendations for preventing TXA drug errors during and immediately after caesarean delivery

| |
|---|
| Raise awareness in health facilities (private and public), both written and verbal. Display a clinical alert warning in operating theatres. |
| Ensure that warnings reach all cadres of staff involved in CDs, whether in an anaesthetic, surgical, nursing or pharmaceutical roles |
| Conduct regular in-service training of all health professionals on how to avoid drug errors. In the SA context, this should be included in the ESMOE/EOST anaesthesia module. |
| Avoid buying drug ampoules that are similar in appearance, and standardise individual drug appearance. |
| Colour-code syringes/drugs where possible. |
| Use bar coding and scanner identification or pre-filled syringes if capacity exists. |
| Physically separate TXA from a dedicated spinal anaesthesia trolley (consider a drug cupboard outside the operating theatre). |
| Ensure appropriate drug checking practices: careful reading of labels with a second person checking, and minimise distractions during medication preparation. |
| Report and review all adverse drug events through an incident reporting system. |
| Minimise staff fatigue. |

TXA = tranexamic acid; CDs = caesarean deliveries; SA = South African; ESMOE = Essential Steps in the Management of Obstetric Emergencies; EOST = Emergency Obstetric Simulation Training.


**Figure 1.** Tranexamic acid, hyperbaric bupivacaine and isobaric bupivacaine.

**Figure 2.** Tranexamic acid and spinal bupivacaine stored in the same container in a private hospital.

trays including bupivacaine, are unlikely to represent solutions for low- and middle-income countries such as SA. Most importantly, the physical location of TXA must minimise the potential for drug error. There are numerous drugs in theatre that should never be injected intrathecally; we need to ensure that TXA is one of these. Avoiding a drug substitution error mandates meticulous attention to drug checking systems, and above all ensuring that TXA is not kept on or near the spinal anaesthesia trolley. Consideration should be given to storing TXA out of theatre, provided that the drug will be available immediately when requested.

We have made recommendations in Table 2 summarising key interventions aimed at reducing drug error from the relevant literature.

Importantly, this clinical alert applies equally to both the private and public sectors in SA, where different versions and appearances of the drug ampoules are available. Figure 1 illustrates the current appearances of TXA and bupivacaine in the state sector in KwaZulu-Natal Province. Figure 2 illustrates the TXA used by one of the private hospitals in KwaZulu-Natal. This image was taken after discovering these ampoules in the same container, illustrating the potential for drug error.

## CONCLUSIONS

The indications for TXA during and after CD continue to expand. The increased use and availability of the drug have led to a concerning increase in inadvertent intrathecal administration worldwide – an error that always results in harm. We need to urgently raise awareness of this potentially lethal mistake and take steps to ensure that we have no further such cases in SA. The first step is to store TXA in a separate location from spinal bupivacaine, and ensure that the drug is never present on the spinal anaesthesia trolley.

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Update in
Anaesthesia

Clinical Article

# Ketamine: Recent Evidence and Current Uses

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## Summary

Ketamine is a versatile drug with a unique profile that allows it to be successfully used for a multitude of situations worldwide. Its variable dosing means it can be used both as an induction agent with a good haemodynamic profile or in lower doses as a reliable sedative or analgesic drug. It has a vital role in prehospital and emergency medicine. As an adjunct during routine anaesthesia it can help reduce opioid requirements postoperatively. Its use in critical care includes sedation and management of refractory asthma; however, further research is required to elucidate its role in trauma and head injury patients. In the developing world, it is a vital and highly valued drug that allows performance of interventions and operations that may otherwise prove impossible, especially when resources are limited.

Ketamine still suffers from traditional stigma from doctors and the public alike and it is often neglected due to concerns about psychological side effects. Increased availability of preparations of pure S-(þ)-isomer ketamine may help increase its popularity.

### KEY POINTS

- Ketamine is a dissociative anaesthetic agent that at differing doses can be utilised as an analgesic, sedative, anaesthetic induction and anaesthetic maintenance agent.
- Ketamine has specific advantages over some of the other sedative and anaesthetic agents. Airway reflexes and tone are often preserved during ketamine sedation and it has an excellent haemodynamic profile.
- Ketamine has a unique role in prehospital, emergency and critical care medicine and is commonly used by anaesthetists all over the world.
- Research has suggested that use of optical isomers of ketamine may help reduce unwanted side effects.
- Ketamine appears to have beneficial anti-inflammatory, bronchodilatory and neuroprotective properties.

## INTRODUCTION

Ketamine is a potent analgesic and dissociative anaesthetic agent that has been used since its discovery and synthesis in 1962. Ketamine's popularity is due to its unique ability to produce rapid sedative, analgesic and amnesic effects together with its beneficial secondary features. The latter include bronchodilation and maintenance of both airway reflexes and sympathetic nervous system tone.[1] Recent studies have also suggested previously unrecognised neuroprotective[2] and anti-inflammatory[3] properties.

Due to ketamine's unique properties and versatility it has gained increasing popularity in prehospital and emergency medicine as well as being used extensively by anaesthetists and anaesthetic assistants throughout the world. Newer uses include low-dose analgesic protocols, adjuvant therapy in local anaesthetic nerve blocks, applications in reactive airways disease, as well as procedural sedation for both routine and complex procedures in theatres, emergency departments and critical care units.

Despite the potential advantages of ketamine, it has not proved universally popular, due to its potentially troublesome "emergence" phenomena, its potential as a drug of abuse and the introduction of other sedative and analgesic drugs.

Research using isomers of ketamine, such as 'S-(+)-ketamine,' a more potent N-methyl-D-aspartate receptor (NMDA) binder, has enabled the use of lower dosing for similar effects.[4] This reportedly results in a lower incidence of the traditional psychoactive side effects, whilst maintaining the beneficial effects of the drug.[5]

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This article will review the pharmacology and varied uses of ketamine with reference to the current literature.

## PHARMACOLOGY

Ketamine is a derivative of the cyclo-hexamine (phencyclidine) anaesthetic agents used extensively in the 1950s. It is a noncompetitive NMDA receptor antagonist, which blocks the phencyclidine binding site on the NMDA receptor thereby stopping depolarisation of the neurone. These NMDA receptors are located at the spinal, thalamic, limbic and cortical levels. Ketamine therefore interferes with sensory input to higher centres of the central nervous system, affecting pain and emotional responses as well as memory, hence it is referred to as a "dissociative anaesthetic."[6] Ketamine also has some secondary effects on opioid receptors, which help to propagate its analgesic effect, as well as catecholamine, alpha and beta receptors.

### Structural Formula

Ketamine (Figure 1) contains a chiral centre at the C-2 carbon of the cyclohexanone ring; this means there are two optical isomers; S-(+)-ketamine and R-(-)-ketamine. The S isomer is pharmacologically more active.

In the UK, ketamine is generally available as a racemic solution, a mixture of R (-) and S (+) isomers in equal amounts. It is available in a variety of concentrations: 10, 50 and 100mg.ml$^{-1}$. Optical-isomer S-(þ)-ketamine (5 and 25mg.ml$^{-1}$ concentrations) is not currently available in the UK but is available in a number of European countries.

## PHARMACOKINETICS

### *Distribution*

Ketamine is highly lipid soluble but has low protein-binding ability. This allows rapid transfer across the blood brain barrier, leading to concentrations there that are generally 4 to 5 times greater than in the plasma. The distribution half-life is around 7 to 11 minutes.

### *Metabolism and Elimination*

Ketamine is mostly metabolised in the liver (80%) into norketamine, which in itself has weak analgesic properties, around 20%to 30% the potency of ketamine. Peak levels of norketamine appear within the blood around 30 minutes after intravenous (IV) administration. Norketamine is then primarily hydroxylised via glucuronoconjugation and excreted in urine and bile.[5]

## PHARMACOKINETICS

### *Central Nervous System*

Ketamine produces a trance-like cataleptic state in which there is potent analgesia and sedation. Emergence symptoms affect 30% to 50% of people. The incidence is more common with higher doses. Symptoms can include a sense of unease, hallucinations, vivid dreams, floating sensations and delirium.

### *Cardiovascular*

Ketamine appears to stimulate the sympathetic nervous system leading to increased cardiac output, tachycardia and increased blood pressure. Therefore, it should be used with caution in those with ischaemic heart disease. The exact mechanism of this is not known; however, it is proposed that ketamine may inhibit reuptake of circulating catecholamines. It has been noted in patients with chronic catecholamine depletion, such as the critically ill, that ketamine alone actually produces a negative inotropic effect. In patients with normal autonomic control the direct negative inotropic effect is often overridden by the central sympathetic response,[1] producing an overall increase or maintenance of blood pressure.[6]

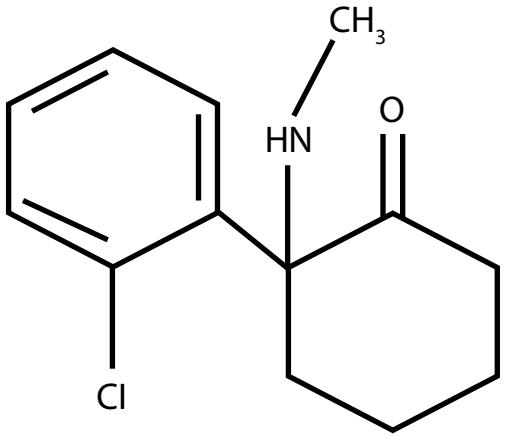


**Figure 1.** Chemical structure of ketamine. There is a chiral centre in the cyclohexanone ring giving the S and R isomers

### *Respiratory*

In contrast to other available sedative and anaesthetic agents, airway tone and both pharyngeal and laryngeal reflexes are often preserved during ketamine use. However, in children younger than 12 months, airway reflexes are more variable and unpredictable.[7] Ketamine may have a slight respiratory depressive effect via a decrease in the usual respiratory stimulant effect of raised $PaCO_2$ levels. This is especially noticeable after administration of large IV boluses, where transient periods of apnoea have been reported.[8] Ketamine has also been shown to cause bronchodilation, making it the induction agent of choice for patients with life-threatening asthma requiring mechanical ventilation.

### *Other Effects*

Ketamine increases muscle tone, blood glucose and plasma cortisol and prolactin levels.[6] A potentially troublesome side effect is increased salivation and some authors advocate coadministration of antisialagogues, commonly atropine.[9]

## USES AND CURRENT EVIDENCE

### *Sedation*

Ketamine is increasingly being used in prehospital and emergency medicine for analgesia and sedation. It is ideally suited for the management of traumatic events such as reduction of fractures and the treatment of burns. The characteristic dissociative state seen with ketamine can be achieved with a dose range between 0.25 and 1.5mg.ml$^{-1}$ IV.

| Route of Administration | Bioavailability | Starting Dose[a] |
|---|---|---|
| Intravenous | 100% | 0.25-1mg.kg$^{-1}$ (adult)[b] |
| | | 0.25-2mg.kg$^{-1}$ (children)[b] |
| | | 1-2mg.kg$^{-1}$[c] |
| Intraosseous | 100% | 0.5-1mg.kg$^{-1}$[b] |
| | | 1-2mg.kg$^{-1}$[c] |
| Intramuscular | 93% | 4-5mg.kg$^{-1}$[b] |
| | | 8-10mg.kg$^{-1}$[c] |
| Oral | 16%-20% | 500 mg max (adult)[b] |
| | | 3-15mg.kg$^{-1}$ (children)[b] |
| Nasal | 45%-50% | 0.25-4 mg.kg$^{-1}$[b] |
| | | 3-9mg.kg$^{-1}$[c] |
| Rectal | 24%-30% | 50mg[b] |
| | | 8-15mg.kg$^{-1}$[c] |

**Table 1.** Routes of administration of ketamine and dose range in children and adults (Reproduced from Marland and Ellerton[4]) The doses quoted above produce a continuum of effects from mild sedation through to full anaesthetic induction. As with administration of any sedative medication, relevant expertise and adequate monitoring is required. In children, variable dosing has been proposed for intranasal, intraosseous and intramuscular routes and there is a lack of consensus in the literature on specific dosing. Examples of paediatric dosing regimes are provided in some of the referenced articles.[29]

**Note:** *a* Ketamine should be titrated to the required clinical effect. *b* Analgesic and sedation dose. *c* Anaesthetic dose.
**Note:** there is some overlap in dosing between sedation and anaesthetic doses.

For procedural sedation in the emergency department, a loading dose administered over 30-60 seconds is recommended. This produces sedation within 1 minute, lasting 5-10 minutes. Large variation exists for recommended loading doses, from 0.25 to 1.0mg.ml$^{-1}$ IV for adults and 0.25 to 2.0mg.ml$^{-1}$ IV for children.[4] It should be noted that doses at the higher range are commonly used for induction of general anaesthesia. A single dose is adequate for shorter procedures, but for longer procedures, the dissociative state can be maintained with intermittent boluses of 0.5mg.ml$^{-1}$. Detailed clinical practice guidelines have been produced for using ketamine in the emergency department[10] but as with the use of any sedative drugs, relevant expertise and adequate monitoring are required. Minimum monitoring, where available, consists of continuous electrocardiogram, non-invasive blood pressure, oxygen saturation and end tidal $CO_2$ monitoring.

Ketamine can be used safely in combination with other drugs such as propofol for induction or sedation. Coadministration of these drugs reduces the required dose of each by around 50%,[4] reducing the incidence and severity of the side effects of both agents. It is proposed that through its sympathomimetic actions, ketamine reduces propofol-induced hypotension, whilst coadministration of propofol reduces the incidence of postprocedure agitation seen with ketamine alone. Randomised control trials have recently shown improved sedation when both drugs are used together compared with propofol alone.[11]

For cases where IV access is difficult, the use of intramuscular, oral or intranasal ketamine has been described with good effect. Time of onset of effect is usually longer for these routes when compared with IV administration and doses required show greater variability due to variations in vascularity and gastrointestinal absorption (see Table 1). Oral use of ketamine, either alone or in combination with paracetamol and diazepam, can be used for dressing changes, especially in burn patients, thus minimising visits to theatre. There is some degree of tachyphylaxis with repeat use.

The main side effects limiting ketamine's use during shorter procedures are agitation and emergence symptoms. Both are more common with higher doses. Benzodiazepines have been shown to be effective at reducing the incidence of emergence phenomena. Use of midazolam (0.07-0.1mg.kg$^{-1}$), diazepam (0.15-0.3mg.kg$^{-1}$and lorazepam (2-4mg) have all been described.[8] Recovering patients in a quiet and controlled environment with ample reassurance has also been shown to reduce the incidence and severity of emergence symptoms following ketamine sedation.

### *Induction and Maintenance of Anaesthesia*

Ketamine is also being increasingly commonly used in hospital and prehospital environments as an anaesthetic induction and maintenance agent for emergency situations. In rapid sequence induction an IV dose of 1 to 2mg.kg$^{-1}$ produces dissociative anaesthesia within 1 to 2 minutes of administration. This is generally longer than the short 'arm-to-brain' time for rapid unconsciousness seen with more traditional IV induction agents such as propofol or thiopentone. However, in circumstances where haemodynamic control is important, such as trauma or sepsis, ketamine has significant advantages. It has also been shown to have other important benefits including allowing for improved preoxygenation in agitated patients when reduced doses (0.25-0.5mg.kg$^{-1}$ IV) may be given prior to full induction of anaesthesia.[12] A reduced dose of ketamine for induction should be considered in shocked patients due to concerns about inadequate sympathomimetic action within this patient group.

**CASE STUDY 1: PREHOSPITAL CARE**

A normally fit and well 6-year-old girl was witnessed to have fallen 6 feet from a wall onto concrete and is complaining of severe pain in her right ankle. She is 45 minutes from the closest hospital and a specialist paramedic ambulance crew is in attendance. She did not lose consciousness and there is no report of any head injury. Primary survey findings are as follows:

<C>: no catastrophic haemorrhage

A + B: Patent airway, self-ventilating, oxygen saturation 99% on air.

C: Haemodynamically stable, all peripheral pulses present but prolonged capillary refill time in her right foot (5 second versus 2 seconds for other peripheries).

D: Glasgow Coma Scale 15, equal and reactive pupils, blood sugar level normal.

E: Fracture dislocation of right ankle, no other obvious injuries.

Due to the diminished perfusion of her foot and the distance from hospital the decision is made to reduce the fracture on scene.

Consider the available options for sedation and analgesia to allow manipulation.

In this case a combination of fentanyl and ketamine was used to induce a dissociative state. After commencement of full monitoring (Electrocardiogram, pulse oximetry non-invasive blood pressure and end tidal $CO_2$) initial doses of 0.5mcg.kg$^{-1}$ of fentanyl and 0.2mg.kg$^{-1}$ of ketamine were given. Gentle traction was applied but this was not tolerated due to pain. Therefore, a further 0.25mcg.kg$^{-1}$ of fentanyl and 0.2mg.kg$^{-1}$ of ketamine was given with good effect, allowing for successful reduction, dressing and splinting with a vacuum splint. Onward transfer was uneventful.

The use of ketamine for total intravenous anaesthesia (TIVA) in combination with muscle relaxants has been described less frequently in the literature. Ketamine use has been reported both as a sole agent and in conjunction with other hypnotics such as propofol and benzodiazepines. Potential indications for ketamine TIVA include cardiogenic shock, hypovolaemia and pericardial tamponade, particularly in low-resource areas where access to vasoactive drugs may be limited. Ketamine TIVA has also been described in paediatric anaesthesia with good effect.[8]

Anaesthesia can be maintained using intermittent boluses of IV ketamine (0.5mg.kg$^{-1}$), or by continuous infusion at 10 to 30mcg.kg$^{-1}$.min$^{-1}$ titrated according to effect. Discontinuing the infusion 20 to 30 minutes prior to the end of surgery allows adequate clearance. It is worth noting that electroencephalography and bispectral index monitoring have no role in monitoring the depth of anaesthesia induced by ketamine.

**Analgesia**

Ketamine is a potent analgesic. It acts as an NMDA antagonist, which as discussed previously, produces dissociative analgesia. However, at lower doses it has been shown to desensitise central pain pathways and modulate opioid receptors.[13] Studies have demonstrated that administration of small doses of ketamine perioperatively can reduce opioid requirements by up to 50%.[14]

Examples of perioperative analgesia regimes include intraoperative ketamine infusions, postoperative infusions, low-dose bolus regimes and patient-controlled analgesia. All have been described in detail in a Cochrane review from 2006.[14] This review provides evidence of the efficacy of perioperative ketamine in providing effective analgesia; however, it does not conclude on optimal dosing or method of delivery. In one randomised controlled trial of postoperative patients following major abdominal surgery who were monitored in the intensive care unit, ketamine was administered with an initial IV bolus of 0.5mg.kg$^{-1}$ followed by an infusion of 2mcg.kg$^{-1}$.min$^{-1}$ for the first 24 hours, followed by 1mcg.kg$^{-1}$.min$^{-1}$ for the next 24 hours.[15] This resulted in a significant reduction of morphine use postoperatively.

In the emergency department and prehospital environment, low-dose ketamine regimes have also been described for pain management. Typically suggested doses are between 0.1 and 0.2mg.kg$^{-1}$ IV. In one study, a bolus dose of 0.1mg.kg$^{-1}$ IV ketamine was given in conjunction with opioids to patients with a variety of presentations, including abdominal pain, lacerations, fractures and dislocations.16 This produced effective analgesia over 120 minutes and reduced opioid requirements and, although some side effects were noted in the group treated with ketamine, most were considered minor and tolerable.

Through desensitisation of central pain pathways, there is some evidence to suggest that ketamine may be helpful in patients undergoing surgery who are chronic opioid users. Several studies in these populations have shown a reduction in opioid use over 48 hours and improved pain scores at 6 weeks following intraoperative IV ketamine.[17] Recently there has also been interest in using intraoperative ketamine to prevent chronic postsurgical pain. A recent meta-analysis looked at studies using low-dose ketamine versus placebo intraoperatively and followed patients up at 3, 6 and 12 months.[18] The results showed postsurgical pain was reduced at 3 and 6 months, although there was no significant difference between

the groups at 12 months. Although initial studies are promising, larger, more rigorous studies are required to explore the potential role that ketamine plays in persistent postsurgical pain.

### Reactive Airways Disease

Ketamine has bronchodilatory effects and has been shown to be effective in patients with acute bronchospasm. Ketamine's effect on the airways is thought to be through modulation of the inflammatory cascade. A recent review has shown that there may be a role for ketamine in asthma that is unresponsive to conventional treatment.[19] The authors noted that patients who received ketamine improved clinically, had lower oxygen requirements and in some cases avoided invasive ventilation. Mechanically ventilated patients who received ketamine for severe bronchospasm showed improved gas exchange, reduced inspiratory pressures, improved minute ventilation and often went on to be successfully weaned off ventilation. No major adverse effects with ketamine were reported in this review of 244 patients. The review included a mix of case reports, case series, observational studies and randomised controlled trials. Highly variable loading doses from 0.1 to 2.0mg.kg$^{-1}$ were used in the studies and depending upon the initial response, the dose used for continuous infusion ranged from 0.15 to 2.5mg.kg$^{-1}$.hr$^{-1}$. Due to the small sample size and wide variety of loading and infusion doses, further research is needed in this area.

### Uses in Critical Care

Ketamine has a number of potential applications within critical care medicine, including sedation, analgesia and the treatment of persistent bronchospasm. Ketofol (ketamine and propofol in combination) has been shown to be effective for short-term sedation in a critical care population.[20] It is important to appreciate that in critically unwell patients ketamine's direct negatively inotropic effect agent may predominate over ketamine's usual positive or neutral cardiovascular response. There have been reported incidents of unexpected decreases in blood pressure and/or cardiac output following ketamine administration in some critically unwell patients; however, a large multicentre study of critically unwell septic patients revealed no adverse effects when using ketamine.[21] It has even been suggested that ketamine may have potential advantages compared to other agents in patients with severe sepsis (see case study 2). There is evidence to suggest that it may exert a protective anti-inflammatory effect, reducing the systemic effects of sepsis including hypotension and metabolic acidosis.[22]

Ketamine was initially thought to be contraindicated in patients with traumatic brain injuries or raised intracranial pressure. However, some studies have shown that ketamine can be helpful as a sedative within these patient groups. Its use has been associated with maintenance of cerebral perfusion pressure during stimulating interventions in a critical care population with brain injuries.[23] Its use in traumatic head injury remains contentious but current evidence (rated Oxford level 2b, GRADE C) suggests that ketamine does not increase intracranial pressure in severe traumatic brain injury patients that are sedated and ventilated and may in fact lower it.[24] Further research is required in this field before its use can be widely recommended.

### Cautions and Limitations

Ketamine is considered to have a very good safety profile. Ketamine overdose has been manifested as prolonged sedation in case studies of children inadvertently receiving 5 to 100 times the recommended dosage.[6] A few isolated case studies of severe respiratory depression have been noted during routine administration of ketamine with other medications; however, mostly only transient apnoeic episodes have been reported following large IV boluses.

Absolute contraindications to IV ketamine as listed by the British National Formulary[25] are hypertension, preeclampsia or eclampsia, severe cardiac disease, stroke, raised intracranial pressure and acute porphyria. Ketamine is also not recommended in children aged, 3 months and in patients with schizophrenia. Please refer to earlier sections within this article for further detail on the use of ketamine in patients with raised intracranial pressure and/or traumatic brain injury.

### Developing World

Ketamine is currently used extensively throughout the world due to its versatility, availability and low side-effect profile. There has been discussion about its potential for misuse and whether greater controls worldwide are required. The World Health Organisation in 2015 concluded that due to the reliance on ketamine in some countries "controlling ketamine internationally could limit access to essential and emergency surgery, which would constitute a public health crisis in countries where no affordable alternatives exist."

### CASE STUDY 2: SEPSIS

A 67-year-old man presents to the emergency department with a 2-day history of productive cough, confusion and fever. He is haemodynamically unstable with hypotension and tachycardia. He is diagnosed with a septicaemia secondary to presumed severe community-acquired pneumonia (CURB65 ¼ 4). Initial treatment consists of IV fluids and appropriate antibiotic therapy. Despite this, his clinical condition continues to deteriorate with worsening hypoxia, hypotension and metabolic acidosis. He is transferred to critical care for commencement of mechanical ventilation and cardiovascular support.

Consider the available induction agents along with the risks and benefits of using each.

In this case, the anaesthetic agent chosen was ketamine at a dose of 1.5mg.kg$^{-1}$. This was because of its cardiovascular stability when compared with alternative induction agents. There is also some evidence to suggest that ketamine has some anti-inflammatory properties.

Ketamine is one of the most available anaesthetic agents in low- to middle-income countries (LMICs).[26] A recent report found that in 12 LMICs, only 53% of facilities had reliable access to a functioning anaesthesia machine and only 52% had continuous access to pulse oximetry. On average 21% to 45% lacked basic airway management equipment. In this survey general inhalational anaesthesia was offered by only 58% of respondents but between 70% and 90% reported reliable access to ketamine.

A study attempting to quantify ketamine use in LMICs found a serious complication rate (i.e., death, cardiac arrest, apnoea, laryngospasm and aspiration) of only 0.15% in over 12,000 administrations of ketamine during routine and emergency surgeries.[27] This low rate of complications was often in the setting of variable practitioner skill and monitoring, suggesting that the safety margin of using ketamine in these situations is high.

Additional examples showing the varied uses of ketamine including use in LMICs can be found in the ATOW 27 by Craven and Alkhafaji.[28]

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Update in
Anaesthesia

Clinical Article

# Complications Associated with Intraoperative use of Irrigation Fluid for Endoscopic Procedures

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**Summary**

With greater understanding of the complications of irrigation fluids and the correlated pathophysiology, anaesthesiologists should be better able to stratify risk and improve the quality of perioperative care.

Irrigation fluid–associated complications, including TURP syndrome, may present subtly, necessitating a low threshold to initiate focused physical examination and investigations. Supportive treatment is the mainstay of initial intervention.

**Key words:**

- A range of fluids are used to improve surgical visibility during endoscopic procedures; examples include saline, glycine, mannitol, and sorbitol solutions.
- Systemic absorption of irrigation fluid can produce a range of electrolyte, cardiovascular, neurological, and other manifestations, depending on fluid type and volume absorbed.
- Rate of fluid absorption is dependent on the pressure gradient between irrigation fluid and blood vessels in the operative field, as well as duration and extent of vascular exposure.
- Transurethral resection of the prostate (TURP) syndrome is associated with hypotonic fluid absorption during TURP and other procedures, causing visual disturbance, headache, nausea, and vomiting, and in severe cases, hyponatraemia, pulmonary oedema, seizures, and coma.
- Measures to reduce the risk of TURP syndrome include monitoring of fluid balance and electrolytes, limiting surgical resection time, and limiting irrigation fluid infusion pressure.
- Management of TURP syndrome is supportive and can include airway support, oxygen, and ventilation, vasopressors, and in severe cases, diuretics, hypertonic saline, and intensive care unit admission.

## INTRODUCTION

With the ever-increasing prevalence of minimally invasive surgical techniques come heightened risks specific to these approaches. While some laparoscopic surgeries use humidified carbon dioxide for insufflation, other procedures such as transurethral resection of the prostate (TURP), transurethral resection of bladder tumour, transcervical resection of endometrium, endometrial ablation, and arthroscopy rely on fluids as primary agents for irrigation and maintenance of surgical visual field.

In the interest of perioperative safety, complications should be anticipated where possible. Understanding the properties and potential risks associated with specific surgical irrigation fluids is the key to guiding management of these complications.

## IDEAL IRRIGATION FLUID

An ideal irrigation fluid should provide a practical and reliable surgical field and cater to the physiological needs of the patient. It should be[1]

- transparent,
- electrically nonconductive for minimal dispersion of diathermy current,
- isotonic and nontoxic to avoid haemolysis and organ impairment through fluid or electrolyte shift, and
- simple and inexpensive to produce and sterilise.

At this time such an ideal solution has not been identified.

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## COMMON IRRIGATION FLUIDS

There are several types of irrigation fluid used commonly in clinical practice. This article will discuss the pharmacology and osmolality of several commonly used irrigation solutions[2] (see Tables 1 and 2).

## CHOICES OF IRRIGATION FLUIDS

Electrolyte-free hypotonic solutions such as glycine, mannitol, and sorbitol solutions are used as distending media to enable monopolar electrical systems to be used for coagulation and tissue resection. However, with the low viscosities, these irrigation fluids bear potential risks of rapid fluid absorption resulting in fluid overload, dilutional hyponatremia, and subsequent side effects. Nowadays, with the advancement in technology, bipolar electrical systems can be used in new operative arthroscopic and hysteroscopic equipment. This enables electrolyte-containing isotonic solutions, for example, normal saline and lactated Ringer solution, to be used as irrigation media. This reduces complications of electrolytes disturbance by irrigation fluids. However, the risks of fluid overload or surrounding tissue oedema remain.

## MECHANISM OF IRRIGATION FLUID ABSORPTION

Rate of fluid absorption is driven primarily by the gradient between irrigation pressure and venous pressure (or the pressure of the operating cavity). In general, irrigation fluid is absorbed at a rate of 10 to 30mL per minute during procedures.[10] Peripheral venous pressure is approximately 1.5kPa and intra-abdominal pressure is 0.5kPa (1kPa ¼ 7.5mmHg). Volume of irrigation fluid absorbed into the circulation increases with time spent with a pressure gradient in excess of 2kPa (15mmHg),[11] and a gradient of 4kPa (30mmHg) has been identified as a threshold for massive absorption.[12] Intravenous infusion of irrigation solutions has been shown to induce tissue oedema. Changes in serum osmolality may reflect this tissue oedema, but only when mannitol is used; glycine and sorbitol enter cells and water will follow so that when these solutions are used, tissue oedema will be greater than suggested by the serum osmolality.

Smoking is an important patient factor known to be associated with large-scale fluid absorption during TURP.[13] Fluid absorption increases with resection extent and longer operation time. The exposure of venous sinuses in the prostate provides ready access of irrigation fluid to the circulation, putting these patients at particular risk. During transcervical resection of the endometrium, fluid absorption is greater if resection of fibroids is performed. Irrigation fluid can be absorbed directly across intact endometrium, as well as being extravasated via the Fallopian tubes,[14] but prior sterilisation does not enhance absorption.

## IRRIGATION FLUID COMPLICATIONS

Complications of endoscopic procedures with irrigation are widely varied and relatively frequent, occurring in around 21% of cases.15 Absorption of irrigating fluids can result in fluid overload. Fluid extravasation into the surrounding tissues can create loco-regional and systemic mass effects. For example, in shoulder arthroscopic surgery, chest wall and neck swelling may lead to airway oedema and respiratory compromise requiring intubation, percutaneous drainage of fluid, diuresis, and the use of steroids. Intra-abdominal fluid extravasation, including abdominal compartment syndrome, has been reported after hip arthroscopy.[16]

Significant uptake of irrigation fluid results in rapid expansion of the intravascular volume leading to fluid overload, as well as dilutional hyponatraemia. This rapidly developing hyponatraemia, if severe enough to cause significant osmotic shift, provokes a net fluid shift away from the intravascular compartment in the brain, resulting in cerebral oedema and raised intracranial pressure. Where glycine is used, hepatic metabolism may result in significantly elevated serum ammonia, which may contribute to neurological deficits in affected patients. It may also provoke seizures by potentiating glutamate activity at the N-methyl D-aspartate receptor, and directly depress the myocardium.

The presentation of TURP syndrome varies, with symptoms developing any time from 15 minutes to 24 hours after the operation.[10] Symptoms include headache, burning sensation in the face and hands, restlessness, and tachypnea. Visual disturbances, such as blurred vision and transient blindness, can occur. If left untreated, patients can deteriorate with features of nausea and vomiting, respiratory distress, pulmonary oedema, confusion, convulsions, and coma.[1] Hypothermia is another important factor to consider in cases of suspected TURP syndrome, given the systemic absorption of large volumes of physiologically hypothermic solutions.[17]

The treatment of TURP syndrome is largely supportive, with early recognition of the developing syndrome being critical to best outcomes. Supplemental oxygen should be provided, with application of positive-pressure ventilation if required for pulmonary oedema. Blood pressure monitoring should be made available via an arterial line and inotropes or vasopressors administered if needed. Affected patients should be warmed if hypothermic and may require antiemetics for nausea and vomiting, or benzodiazepines for seizures. Serum sodium should be corrected slowly and monitored closely. Concurrent diuresis might have an impact on the rate of sodium correction and should be done with caution. A 4 to 6mmol/L increase in serum sodium concentration is adequate in the most seriously ill patients in a 24-hour period.[18] Hypertonic saline (3%) is indicated when there is severe hyponatremia (some authors1 have suggested, 120mmol/L). Diuretics are usually only used when acute pulmonary oedema is prominent because both mannitol and furosemide can cause sodium loss and worsening hyponatraemia.

Similar presentations can be seen in other procedures utilising irrigation fluid, such as transcervical resection of the endometrium.[2]

In the event of any serious complication, the anaesthesiologist should ensure clear documentation of the incident and treatment responses. The anaesthesiologist should take part in further discussion with the surgeon on the risk factors involved and should advise on future management during endoscopic surgery. Clear communication with the patient and relatives regarding the event is important.

## MEASURES TO MINIMISE COMPLICATIONS

Minimising negative outcomes relies on limiting the absorption rate of irrigation fluid, recognising complications early, and providing prompt resuscitation.

**Table 1.** Pharmacology of Common Irrigation Solutions Abbreviations: $T_{1/2}$, half-life; $T_{1/2}$ dist, distribution half-life; $T_{1/2}$ elim, terminal half-life; CNS, central nervous system; NMDA, N-methyl D-aspartate; TURP, transurethral resection of the prostate; TCRE, transcervical resection of endometrium

| **Solution: Indications for Use** | **Pharmacokinetics** | **Pharmacodynamics** |
|---|---|---|
| **Normal saline:** arthroscopy, transurethral procedures | • $T_{1/2}$ ¼ 110 minutes[3]<br>• Iso-osmotic with the extracellular fluid<br>• Distributed 25% intravascularly and 75% in interstitial fluid | • It contains more chloride than extracellular fluid. Sodium remains extracellular because of the sodium pump. Rapid infusion of large amount of normal saline could cause hyperchloraemic acidosis.[4] |
| **Lactated Ringer solution:** arthroscopy | • $T_{1/2}$ ¼ 50 minutes<br>• Hepatic metabolism of lactate by gluconeogenesis (70%) | • Hydrogen ions are consumed and a relative excess of bicarbonate ions is produced reducing acidosis in a controlled fashion.<br>• Some critically ill patients may develop alkalosis and hypokalaemia due to failure to excrete excess bicarbonate from lactate metabolism.[5] |
| **Glycine 1.5%:** TURP or TCRE | • $T_{1/2\ dist}$ ¼ 6 minutes (dose-dependent due to intracellular accumulation)<br>• Limited penetration into the CNS<br>• $T_{1/2\ elim}$ 40 minutes to several hours<br>• Hepatic metabolism to ammonia<br>• 5%–10% of an infused load is excreted unchanged by kidneys | • Glycine is the second most widespread amino acid in human enzymes and proteins. It is an important inhibitory neurotransmitter in the CNS and retina.<br>• Glycine toxicity may cause prickling sensations, facial warmth, headache, nausea, malaise, and retinal dysfunction including transient blindness.[6]<br>• Glycine may directly provoke myocardial depression.<br>• Glycine potentiates the NMDA receptor, which may precipitate convulsions and encephalopathy.<br>• High serum ammonia levels may result in neurological disturbance.<br>• Glycine protects against kidney injury induced by a brief period of ischemia in laboratory animals, but it does not attenuate severe renal damage caused by longer periods of ischemia.[7] |
| **Mannitol 3%:** TURP or other transurethral procedures | • $T_{1/2\ dist}$ ¼ 10 minutes; spread throughout extracellular space<br>• $T_{1/2\ elim}$ approximately 100 minutes<br>• Renal excretion which promotes osmotic diuresis (prolonged T1/2 in patients with renal impairment) | • Mannitol rapidly expands intravascular volume and can potentially lead to fluid overload, pulmonary oe-dema, and cardiac failure in susceptible patients.<br>• Elevated plasma concentration can be associated with bradycardia and hypotension.<br>• Some studies found few symptoms after absorption of mannitol 5%; this is possibly due to the isotonic nature of the more concentrated solution.[8]<br>• Allergic reactions to mannitol are rare. |
| **Sorbitol 3.5%:** urologic irrigation fluid | • $T_{1/2\ dist}$ 6 minutes<br>• $T_{1/2\ elim}$ 33 minutes<br>• Hepatic metabolism to fructose and lactate<br>• 5%–10% of an infused load undergoes renal excretion | • Unabsorbed ingested sorbitol can provoke diuretic and laxative effects.<br>• Excessive intravenous administration may cause hyperglycaemia, or potentially lactic acidosis from its metabolite fructose.<br>• Paradoxically, hypoglycaemia can develop in young patients with fructose-1,6-diphosphatase deficiency.[9] Sorbitol infusion has led to death in patients with fructose intolerance due to aldolase B enzyme insufficiency. |

**Table 2.** Physical Properties of Common Irrigation Solutions [a]Tonicity: the measure of the osmotic pressure gradient between two solutions, only influenced by solutes that cannot cross the semipermeable membrane. [b]Osmolality: the measure of solute concentration per unit mass of solvent.

| Solution | Concentration (%) | Tonicity[a] | Osmolality[b] |
|---|---|---|---|
| Saline | 0.9 | Isotonic | 308 |
| Saline | 3 | Hypertonic | 900 |
| Lactated Ringer | - | Isotonic | 273 |
| Glycine | 1.5 | Hypotonic | 220 |
| Mannitol | 3 | Hypotonic | 179 |
| Mannitol | 5 | Isotonic | 298 |
| Sorbitol | 3.5 | Hypotonic | 165 |

General principles include the following:

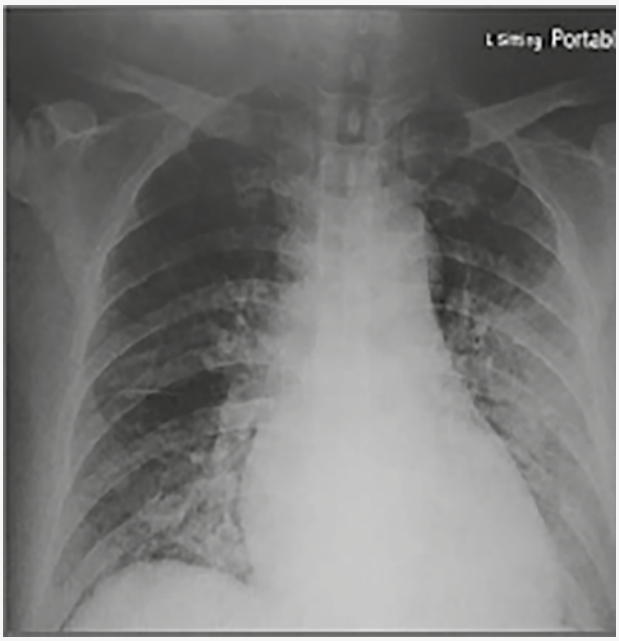
- Ensuring adequate fluid status and using vasopressors such as phenylephrine to maintain venous pressure. Low venous pressure enhances irrigation fluid absorption.
- Reducing operative duration where possible, preferably limiting it to less than 1 hour.
- Delivering irrigation fluid at the lowest required pressure, and warming where possible. Using warmed irrigation fluid does not increase blood loss by regional vasodilation.
- Monitoring of perioperative fluid balance is of paramount importance. Vigilance for early signs of mass effect and fluid overload should reduce perioperative morbidity.
- Using meticulous surgical techniques to avoid fluid extravasation and visceral perforation and minimise blood loss.

Traditionally, spinal anaesthesia was thought to be beneficial compared to general anaesthesia, though little evidence supports any significant difference in outcomes between the two techniques.

## CASE SCENARIO

A 54-year-old man with carcinoma of the bladder was scheduled for a transurethral resection of a bladder tumour. He was obese and had a history of a prior stroke. His baseline serum sodium was 137mmol/L. He was very anxious about the procedure and refused a neuraxial block. The surgery therefore proceeded under general anaesthesia. The operation duration was 75 minutes. This was partly due to the extensive bladder infiltration by carcinoma which required more traumatic resection. Glycine 1.5% solution was used as irrigation fluid. A net irrigation fluid balance of þ1.6 L was noted, though intraoperative irrigation pressure was not documented. Minimal blood loss was reported, and the surgery was considered uneventful by the surgeons. Only 500mL of intravenous 0.9% saline was given intraoperatively. Reversal of neuromuscular blockade was given when a train-of-four count of 3/4 was achieved. Restlessness and respiratory distress were noted shortly after extubation.

The patient was postured upright in a sitting position and was found to be responsive to supplemental oxygen. His oxygen saturation reached 88% to 92% with oxygen delivered at 8L/min via Hudson mask, and increased to 95% with 100% oxygen via a non-rebreather mask. Wheeze was noted throughout his left chest and ABG showed type 1 respiratory failure with mild metabolic acidosis (Table 3).



The patient was treated with inhaled salbutamol and 10 mg of intravenous furosemide. His oxygen requirements diminished, saturating at 95% on 6L/min and he was transferred to the intensive care unit for ongoing management without need for reintubation.

A chest x-ray was ordered and showed obscured bilateral lower lung fields consistent with pulmonary oedema (Figure 1). Postoperative blood results showed serum sodium 128mmol/L, potassium 3.5mmol/L, and haemoglobin 85g/L. He was put on fluid restriction in the intensive care unit, with maintenance of 0.9% NaCl titrated to serum sodium level.

**Table 3.** ABG Results

1. pH 7.35
2. Base excess -3mmol/L
3. Bicarbonate 22.4mEq/L
4. $pO_2$ 48mmHg, $SaO_2$ 82%
5. $pCO_2$ 40.6mmHg

In this scenario, the patient developed hyponatremia with pulmonary oedema after transurethral resection of a bladder tumour. There were several risk factors identified for fluid overload. The operation lasted more than 60 minutes. The prolonged operation increased this patient's exposure to continuous irrigation with associated increased fluid absorption. Additionally, the unanticipated extent of the surgical insult may have exposed more blood vessels for circulatory absorption. Failure to recognize the pathology may have led to further deterioration with seizures and shock.

Early recognition of the extent of the bladder tumour may have prompted more meticulous monitoring and heightened communication with the surgeon around the recognised risk. This may have prompted the team to take extra precaution by minimising irrigation pressures and surgical trauma. In this case, the choice between a general or regional technique was complicated by a history of anxiety. The use of regional anaesthesia may have allowed earlier detection of hyponatremia and pulmonary oedema through clinical signs such as change in conscious level and difficulty in breathing. Where general anaesthesia is unavoidable, intraoperative vigilance should be employed, observing for increase in airway pressure or oxygen requirement. Point-of-care monitoring including ABG and electrolytes may assist in providing an early and more complete picture of the patient's physiological state.

Spinal anaesthesia offers advantages in monitoring and postoperative analgesia. The ability to detect early signs of TURP syndrome makes spinal anaesthesia the technique of choice for many anaesthesiologists.

Laser techniques for TURP are gaining popularity. The reduced risk of bleeding and the use of saline as irrigation fluid, make this a favourable technique, particularly for elderly or debilitated patients. A review of monopolar versus bipolar TURP has shown bipolar TURP offers some advantages over monopolar TURP, including reduced incidence of TURP syndrome related to avoidance of hypotonic irrigation solutions.[19]

Patients' blood pressure, oxygen saturation, and electrocardiograms should be monitored in the standard way. When alert, patients' complaints and changes in mental status may be the first signs of early electrolyte imbalance. Information on patients' vital signs, input and output of irrigation fluid, blood loss, and investigation results (blood glucose, electrolytes, haemoglobin, arterial blood gases [ABG], and ammonia) should be collected and analysed if clinical concern of evolving TURP syndrome develops. Exhaled or serum ethanol concentration can also be measured as an index of fluid absorption in cases in which ethanol has been added to the irrigation fluid.[20] Upon suspicion of deterioration, supportive treatment should be commenced, and potential causes investigated.

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Update in
Anaesthesia

Case Report

# Posterior Reversible Encephalopathy Syndrome (PRES)

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## DEFINITION

Posterior Reversible Encephalopathy Syndrome (PRES) is a clinico-radiological syndrome of heterogeneous etiologies that are grouped together because of similar findings on neuro-imaging studies.

It was first described by Hinchey et al. in 1996 based on 15 cases[1]

This condition has been known by various names previously (reversible posterior leukoencephalopathy syndrome, reversible posterior cerebral edema syndrome and reversible occipital parietal encephalopathy). PRES is now the widely accepted term.[2]

This clinical syndrome is increasingly recognized commonly because of improvement and availability of brain imaging.

### Pathophysiology

There are two main hypotheses; one involves impaired cerebral autoregulation responsible for an increase in cerebral blood flow (CBF), whereas the other involves endothelial dysfunction with cerebral hypoperfusion. Under both hypotheses, the result of the cerebral blood perfusion abnormalities is blood brain barrier dysfunction with cerebral vasogenic edema.[2]

### Clinical findings

It presents with rapid onset of symptoms including headache, seizures, altered consciousness, and visual disturbance. It is often associated with acute hypertension.

PRES is most commonly occuring with preeclampsia, eclampsia, hypertensive crisis, sepsis, autoimmune disease, cytotoxic chemotherapy, and transplantation.[3]

### Radiological findings

PRES has become synonymous with a unique pattern of brain vasogenic edema seen on CT or MR brain imaging studies. It was believed to consistently produce bilateral and symmetric regions of edema typically located in the white matter and predominating in the posterior parietal and occipital lobes[4], hence the name. Recently, it was found to present in a variety of radiological patterns;[2]

1. Holohemispheric watershed pattern; showing bilateral vasogenic edema in a linear pattern involving the white matter of the cerebellum, brain stem, occipital, parietal, frontal and temporal lobes.
2. Superior frontal sulcus pattern; showing bilateral vasogenic edema in a non-confluent patterns involving the frontal sulcus area and, to a lesser degree, the white matter of the parietal, occipital, and temporal lobes.
3. Dominant parietal-occipital pattern 'the classic pattern'; showing bilateral vasogenic edema in the white matter of the occipital and parietal lobes.
4. Partial and/or asymmetric expression of the three primary patterns.

### Differential Diagnosis

The non-specific clinical manifestations and multiplicity of radiological patterns raise diagnostic challenges. Many conditions may resemble PRES including;[2]

1. Ictal or post-ictal state (with or without status epilepticus),
2. Progressive multifocal leukoencephalopathy (PML),
3. Severe leukoaraiosis,
4. Cerebral autosomal dominant arteriopathy with subcortical infarcts,
5. Infectious encephalitis,
6. Acute disseminated encephalomyelitis,

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7. Mitochondrial myopathy encephalopathy lactacidosis and stroke-like episodes syndrome (MELAS),
8. Vasculitis,
9. Creutzfeld-Jakob disease,
10. Cerebral venous sinus thrombosis,
11. Ischemic stroke (watershed or posterior cerebral artery territory).

**Prognosis**

If promptly recognized and treated, the clinical syndrome usually resolves within a week, and the changes seen in magnetic resonance imaging (MRI) resolve over days to weeks. Patient usually recovers but permanent disability is possible.[5]

**Case Report**

A 34-year-old female presented to the emergency department 5 days after uneventful normal delivery complaining of neck pain and headache. The patient did not receive epidural analgesia for her delivery. She has no medical or surgical history of significance.

Blood investigations revealed raised WCC (12.7/uL), CRP (51.9mg/L) and D-dimer (19.8ug/ml). She had been discharged home after 2 days as all investigations including CSF analysis, CTPA and MRI brain appeared to be normal.

3 days later, she was brought again to emergency department with 2 episodes of tonic clonic convulsions and hypertension with protein in urine of +1. MRI was done showing multifocal vasogenic edema in the subcortical white matter consistent with posterior reversible encephalopathy syndrome (PRES).

The patient symptoms had improved over 3 days of receiving treatment in the intensive care unit with anticonvulsants and antihypertensives. She was then transferred to the normal ward where she repeated MRI brain which revealed significant improvement of radiological picture.

**Management**

Management of the syndrome is focused on the treatment of the underlying condition (e.g. eclampsia) and supportive treatment such as anticonvulsive agents.

**Discussion**

Posterior reversible encephalopathy syndrome (PRES) diagnosis basically depends on specific radiological features and clinical findings. The exact pathophysiological mechanism of the syndrome is still not fully understood but it may be explained by disruption of endothelial blood - brain barrier which leads to fluid and protein transudation in the brain.

High level of suspicion and early management are the key elements of recovery.

Although our case did not suffer of pregnancy related hypertension or preeclampsia during her pregnancy, hypertension was discovered on the 10th day post-delivery after her second presentation to A&E. This raises the concern of following up parturients post-delivery for the possible development of new onset preeclampsia. It is worth mentioning that preeclampsia can present as late as 4 to 6 weeks postpartum according to American College of Obstetricians and Gynecologists guidelines.[6]

PRES can be one of the complications that could result from untreated preeclampsia. Better outcome can be attained by early diagnosis and prompted treatment.

## CONCLUSION

PRES should be considered in patients who present with seizures, altered consciousness, visual disturbance, or headache, particularly in the context of acute hypertension. It should not be missed as one of differential diagnoses of postpartum headache and convulsions. Fortunately, if it is promptly recognized and treated, the clinical syndrome usually resolves within a week.

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Update in
Anaesthesia

Letter

# OxyContin: A Tale of Advertisement and Addiction

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## Summary

Purdue Pharma is under scrutiny for its role in North America's opioid crisis with its widely marketed narcotic OxyContin. Released in 1995, the same year as the American Pain Society announced their Pain is the Fifth Vital Sign campaign, OxyContin quickly became a blockbuster drug through aggressive advertisement. Purdue Pharma sponsored tens of thousands of pain management education programs, funded influential organizations, and marketed directly to physicians. They publicized research that downplayed the risk of addiction, suppressed early reports of drug abuse, and led physicians to believe that iatrogenic narcotic addiction was rare. By 2004, OxyContin had become the most prevalent prescription opioid abused in the USA.

Purdue Pharma has since acknowledged misleading regulators, doctors and patients about OxyContin's risk of addiction and abuse. The company recently filed for bankruptcy, as thousands of jurisdictions are now seeking to recover costs associated with the opioid crisis. This story demonstrates how vulnerable physicians are to marketing and misinformation, and the importance of critical appraisal when new drugs, technologies, and practice patterns are introduced to our practice.

## Key Words

Opioid epidemic, oxycodone, opioid-related disorders, analgesia, advertising

Purdue Pharma is widely scrutinized for its role in North America's opioid crisis. How its blockbuster opioid OxyContin came to generate over $31 billion in revenue is a story of how physicians, the public, and medical institutions are vulnerable to marketing and misinformation.

In the 19th century, opioids were in vogue for ailments including pain, insomnia, diarrhea, and cough. The early 20th century saw advances in public health and the invention of nonopioid analgesics. Iatrogenic opioid dependence became a concern in the 1920s; opioid overprescribing was considered a hallmark of the out of date physician.[1] By the 1980s, clinicians began to question whether their pain management was adequate. Purdue released OxyContin, a long acting oxycodone, in 1995. In the same year, the American Pain Society announced their Pain is the Fifth Vital Sign campaign, urging healthcare providers to take pain as seriously as other vital signs. The Veteran's Health Association, the largest healthcare system in America, adopted the campaign in 1999. The Joint Commission, which accredits hospitals in the US, announced pain management standards emphasizing the use of quantitative pain assessments. Physicians to prescribe more opioids. After implementation of a mandatory pain score in the Mayo Clinic Hospital PACU, opioid use increased on average from 6.5 to 10.5mg of morphine equivalents.[2] Purdue Pharma's revenues soared.

Purdue Pharma funded over 20,000 pain-related educational programs between 1996 and 2002. They provided financial support to influential organizations including the American Pain Society and the Joint Commission. OxyContin was extensively marketed directly to physicians. Purdue advertised in medical journals, sponsored pain websites, and recruited specialists to spread word about an epidemic of untreated chronic pain. They sent pharmaceutical representatives across the country to provide samples and distribute branded marketing products. From 1997 to 2002, the annual number of OxyContin prescriptions for cancer increased from 250,000 to over 1 million; prescriptions for noncancer pain increased from 670,000 to 6.2 million.[3]

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Purdue promoted OxyContin as less addictive and less prone to abuse than other opioid medications due to its controlled release mechanism. They promoted literature that downplayed the risk of addiction to opioids. A 1980 paper by Porter and Jick was heavily referenced.[4] Only 5 sentences long, this study has been cited over 600 times and has its own Wikipedia page.[5] In 12,000 inpatients who received narcotics, "there were only four cases of reasonably well documented addiction". Their study used healthcare provider documentation to define addiction instead of applying diagnostic criteria, thereby underestimating its prevalence. The subjects were inpatients who received as little as a single narcotic dose administered by hospital personnel. In contrast, most patients using OxyContin self-medicated at home over long periods of time. Despite the lack of external validity, Purdue cited the risk of addiction as less than 1%. The original OxyContin package insert stated that iatrogenic addiction to opioids legitimately used in the management of pain is "very rare".[6]

A later investigation found that Purdue Pharma's sales representatives had written the words "street value," "crush," or "snort" in 117 internal notes from visits to medical professionals from 1997 to 1999, suggesting they were aware of abuse as early as 1997.[7] By early 2000, media reports of OxyContin abuse surfaced. Users evaded the controlled release mechanism by crushing the tablets and snorting or dissolving and injecting them. Purdue Pharma created a plan to combat abuse, but significant damage had already been done. The Drug Enforcement Agency reported 146 deaths nationally involving OxyContin in 2000 and 2001.[3] By 2004, OxyContin was the most prevalent prescription opioid abused in the USA.6 In Canada, the addition of long-acting oxycodone to provincial drug formularies was associated with a 5-fold increase in oxycodone-related mortality between 1994 to 2004.[8]

In 2010, Purdue Pharma released a tamper resistant OxyContin. Abuse decreased by 48% in the three years following reformulation; overdose fatalities reported to the manufacturer decreased by 65%.[9] However, reformulation may have had collateral damage. A survey of 10,000 patients with opioid use disorder found that heroin use increased after reformulation; reformulation perhaps hastened the transition from prescription opioid to heroin abuse.[10] In Canada, long acting oxycodone was dropped from provincial drug formularies in 2012. The next year, Canada's first fentanyl seizure occurred when police arrested two men shipping a microwave containing 10,000 fentanyl tablets. In 2017, there were almost 4,000 opioid related deaths in Canada; 72% involved fentanyl or fentanyl analogues. One form of street fentanyl is put through a pill press and dyed green to resemble 80mg OxyContin tablets.[11]

Legal action against Purdue Pharma gathered momentum. In 2007, three Purdue executives and Purdue Frederick, a Purdue Pharma holding company, pled guilty to criminal charges that they had misled regulators, doctors and patients about OxyContin's risk of addiction and abuse. Perdue Frederick paid $600 million in fines; the executives paid $34.5 million.[7] As of 2019, 48 of 50 US states have sued Purdue Pharma.[12] Municipalities, counties, and first nations tribes have also filed lawsuits. Over 2600 lawsuits against the company and their owners, the Sackler family, were bundled into a giant civil case in federal court. In September 2019, a tentative agreement was reached: Purdue Pharma would be dissolved; a publicly overseen company would sell OxyContin and pay the plaintiffs with the profits. Purdue would donate drugs for addiction treatment and overdose reversal. The Sackler family would pay $3 billion over 7 years. The deal is estimated to be worth $10 to 12 billion.[13] Purdue Pharma subsequently filed for bankruptcy; further negotiations are ongoing.

The story of OxyContin provides insight into our medical culture and how easily influenced we are as healthcare practitioners. It demonstrates the importance of critical appraisal when new drugs, technologies, and practice patterns are introduced in order to best serve our patients. Many patients are first exposed to opioids perioperatively; the incidence of new persistent opioid use after surgery is 5.9 to 6.5%.[14] It is the author's hope that revisiting the story of OxyContin and Purdue Pharma will serve as a learning opportunity for our community.

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Update in
Anaesthesia

Letter

# Sphenopalatine Ganglion Block: Management of Post-dural Puncture Headache After Cesarean Section

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## Abstract

The sphenopalatine ganglion is a parasympathetic ganglion and has been blocked for various types of headaches and facial pain. We have reported a patient with severe post-dural puncture headache after cesarean section who showed rapid symptomatic improvement after a single sphenopalatine ganglion block.

## Dear Editor

The Sphenopalatine ganglion (SPG) is a parasympathetic ganglion. SPG block has been applied for various types of headaches and facial pain.[1-3] Here, we report a patient with severe post-dural puncture headache (PDPH) after cesarean section who showed rapid symptomatic improvement after a single sphenopalatine ganglion block. The written consent from the patient for this case report to be written up as well as for her photograph to be taken has been obtained.

The patient was a 22 year-old pregnant woman (165 cm, 68kg) at 37 weeks' gestation, who underwent emergency cesarean delivery. She ate her last meal 15 minute prior to the surgery. Informed written consent was obtained for spinal anesthesia. Spinal anesthesia was performed with a 25G Quincke spinal needle at the L3–L4 interpace with heavy bupivacaine 0.5% 13mg.

The patient complained of a severe headache on the first postoperative day. The visual analog scale (VAS) score was evaluated as 10/10 and aggravated by movement. After detailed examination a diagnosis of PDPH was made. Movement was restricted and bed rest was prescribed. Paracetamol 1gram and 50 mg caffeine orally every 6 hours was administered, as well as an intravenous infusion of 200mg theophylline were administered. Normal saline infusion was started at the rate of 2ml/kg/h. However, the next day the patient showed no improvement of symptoms and was agitated. SPGB was suggested to the patient. After obtaining written consent, the patient was made to lie in the supine position with her neck slightly extended. SPG block was performed by a trans-nasal approach. A total of 2 puffs of Lidocaine 10 % spray was applied through both nares with an applicator. (Figure1). Approximately 5-10 minute after the trans-nasal injection the patient described significant relief of symptoms of her headache. The VAS score was evaluated as 0/10. The following day the patient was able to sit up and eat. The patient remained in hospital for 4 days with no further complaint of headache.

The sphenopalatine ganglion is located in the pterygopalatine fossa posterior to the middle turbinate. The tip of the applicator does not come into direct contact with ganglion, but the local anesthetic infiltrates around it. The connective tissue and mucus membrane make topical application of local anesthetic effective. [4] After dural puncture cerebrospinal fluid is lost continuously. Compensatory vasodilation occurs and this vasodilatation causes a headache. If the parasympathetic activity is blocked with a SPG block uncontrolled vasodilation is prevented and patients feel symptomatic relief. [5] Trans nasal SPG block is an effective technique for pain control in patients with PDPH and this technique appears to be a simple, generally safe method. It, however, needs further study and investigation regarding its efficacy.

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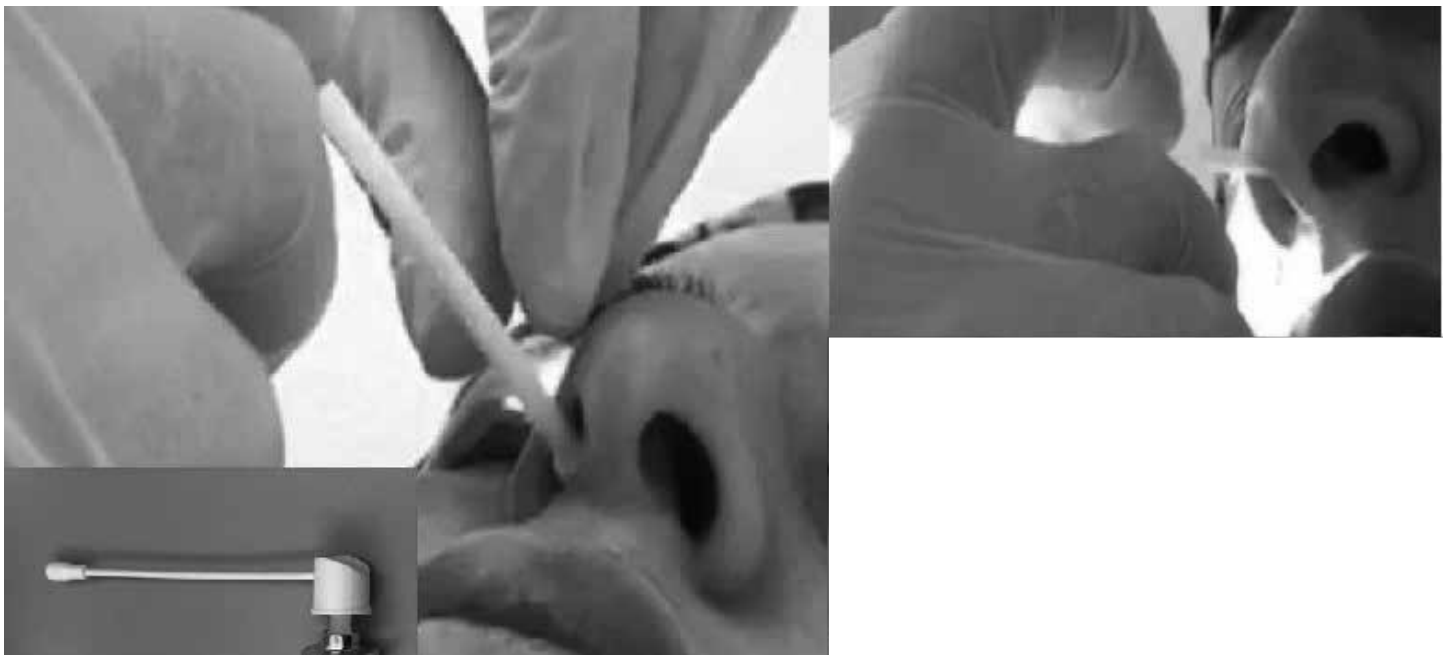
**Figure 1.** Position of applicator in the nare



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Update in Anaesthesia

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## GENERAL CONSIDERATIONS FOR PREPARATION AND SUBMISSION OF A MANUSCRIPT

A major focus of UIA is to provide educational materials for those working with limited resources. The types of manuscripts that are published in the journal reflect this. If you have an idea for an article and would like to discuss this further, please email the Editor-in-Chief with a proposed title and a brief (200 word) summary of the scope and content.

Manuscripts are screened by the editorial staff and are sent to independent reviewers who are not informed of the identity of the author(s). The reviewers' comments and suggested revisions will be forwarded to the corresponding author. Manuscripts will be reviewed with plagiarism detection software. Manuscripts may not have been published in whole or any part in another journal.

Some readers of UIA may not use English as their first language. It is therefore important to keep text straightforward and to avoid long sentences and complex terminology. Explain words and abbreviations that may not be universally standardised.

Aim to include the full range of therapies available worldwide. Provide detailed descriptions of therapies available in resource-limited settings. When appropriate, discuss older medications, such as Halothane and Thiopentone that may still be used around the world.

Authors must acknowledge any financial support received or conflict of interest related to the contents of a submitted manuscript.

Contributions to the, 1) clinical care or research described in a manuscript or 2) preparation of a manuscript made by persons other than the authors may be acknowledged.

Upon acceptance for publication copyright becomes vested with the journal.

Manuscripts based on clinical investigation of human subjects must adhere to the ethical principles of the Declaration of Helsinki developed by the World Medical Association. **https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/**

Manuscripts based on clinical investigation of human subjects must include the consent of the patients or study participants or appropriate person (parent/guardian) and a statement of approval from an appropriate Institutional Review Board (IRB)/Ethics Committee. The IRB/Ethics Committee must review and provide oversight or grant exemption from requiring patients' or study participants' consent for the performance of audits and this should be referred to in the text.

Manuscripts must protect patients and study participants from being identified. UIA adheres to the USA HIPAA Privacy Rule that defines 18 identifiers that must be removed to assure the protection of personal health information. **https://privacyruleandresearch.nih.gov/pdf/HIPAA_Privacy_Rule_Booklet.pdf (Specifically refer to page 10)**

Manuscripts should adhere to Uniform Requirements for Manuscripts Submitted to Biomedical Journals prepared by the International Committee of Medical Journal Editors. **http://www.icmje.org/recommendations/browse/manuscript-preparation/preparing-for-submission.html**

### Manuscript Types

As an official journal of the WFSA, UIA is the appropriate forum for publication of articles describing anaesthesia patient care, original research and audit conducted in, and specifically relevant to, low and middle income resource settings.

Manuscripts describing clinical care, research, procedures, techniques or equipment adapted by anaesthetists to the limited resource setting in which they care for patients are welcome in any of the following formats:

- Review article - Basic Science or Clinical (3000 words maximum)
- Original Research (3000 words maximum)
- Case Report/Clinical Overview (1500 words maximum)
- UIA Short Reports (750 words maximum)
- Editorials (1200 words maximum) - Editorials are usually by invitation of the Editor-in-Chief. Proposals for Editorials may be sent to the Editor-in-Chief for consideration and potential invitation.
- Review of Books or other Educational Materials (eg web app) (750 words maximum)

- Letters to the Editor (1000 words maximum) - Correspondence is welcome on any topic, article or editorial that has appeared in UIA or is of interest to individuals providing anaesthesia patient care.

## COMPONENTS OF THE MANUSCRIPT

Title page that includes:

- Title of the article
- Name and affiliation of each author
- Email, postal address and telephone contact details of the corresponding author
- Key words using terms from the Medical Subject Headings (MeSH) of Index Medicus https://www.nim.nih.gov/mesh
- Abstract that includes no more than 200 words

For research manuscripts note Background, Methods, Results, and Conclusions

## ILLUSTRATIONS / FIGURES

Tables, figures, graphs and illustrations should be submitted as electronic versions of drawings (black on white) or as black and white or color picture files in JPEG format. If computer or internet access is unavailable, print versions may be submitted. If facilities to produce drawings are unavailable, contact the Editor-in-Chief for assistance. Text accompanying tables, figures, graphs and illustrations should be supplied on a page separate from the image.

Tables, figures, graphs and illustrations copied from other publications must be accompanied by a statement that permission for reproduction has been obtained from the publisher. A footnote acknowledging permission to reproduce must accompany the copied table, figure, graph or illustration and the full reference of the original source included in the reference list.

If patients appear in an identifiable photo, a copy of their consent to the use of their image must be submitted.

## REFERENCES

A minority of UIA readers have extensive access to journals. References, therefore, should in general be limited to those that are considered 'desirable supplemental reading', and should not exceed 25 references. Number the references in the order they appear in the text, using the reference number as a superscript at the relevant point in the text.

Reference style should adhere to the format set forth in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals prepared by the International Committee of Medical Journal Editors http://www.icmje.org

Abbreviations for journal titles should follow Index Medicus format https://www.ncbi.nlm.nih.gov/nlmcatalog/journals

Examples of the recommended format for references are noted below and can be found at https://www.nlm.nih.gov/bsd/uniform_requirements.html

1. Reynolds F, O 'Sullivan G. Lumbar puncture and headache. 'Atraumatic needle' is a better term than 'blunt needle'. Br Med J 1998; 316: 1018.
2. Costigan SN, Sprigge JS. Dural puncture: the patients' perspective. A patient survey of cases at a DGH maternity unit 1983–1993. Acta Anaesthesiol Scand 1996; 40: 710–14.
3. Spriggs DA, Burn DJ, French J, Cartlidge NE, Bates D. Is bedrest useful after diagnostic lumbar puncture? Postgrad Med J 1992; 68: 581–3.

References to textbooks should give book title, place of publication, publisher and year; those of multiple authorship should also include chapter title, first and last page numbers, and names and initials of editors. For example:

1. Roberts F. Chapter 22: Ear, nose and throat surgery. In: Allman KG, Wilson IH, eds. Oxford handbook of Anaesthesia (1st edition) Oxford: Oxford University Press, 2001: 506-39.

Unpublished manuscripts in preparation or submitted yet not accepted for publication and personal communications and unpublished observations should be referred to as such in the text.

Articles accepted and not yet published should be included in the references, with the abbreviated journal name, followed by '(in press).

## MEDICATIONS

Use international units, e.g. mg.kg -1 rather than mg/kg. Use SI notation for g, mg, mcg etc. Use internationally accepted non-proprietary generic medication names, e.g. furosemide, epinephrine and avoid trade names.

Manuscripts should be submitted to:

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UIA's Editorial Team will be delighted to help with the preparation of articles. Please contact the Editors-in-Chief for any assistance.

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If you are unable to upload your manuscript to the online submission system, please email them directly to the editors.

Alternatively manuscripts may be sent to:

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