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CSF LAVAGE AS A RESCUE MANEUVER FOR REFRACTORY INTRATHECAL MORPHINE TOXICITY FOLLOWING TOTAL ABDOMINAL HYSTERECTOMY PROCEDURE

Anaesthesiology

Dr Vishnu Datt*	Professor & HOD Anaesthesiology and critical care, SGT Medical college, Gurugram, Haryana, India. *Corresponding Author
Dr Sakshi Dhingra	MD Student, Anaesthesiology and critical care, SGT Medical college, Gurugram, Haryana, India.
Dr Shreya Khatri	MD Student, Anaesthesiology and critical care, SGT Medical college, Gurugram, Haryana, India.
Dr Simran Yadav	MD Student, Anaesthesiology and critical care, SGT Medical college, Gurugram, Haryana, India
Dr Rashmi Ray	Professor of Gynae & Obs, SGT Medical college, Gurugram, Haryana, India.
Dr. Palak Arora	MD Student, Anaesthesiology and critical care, SGT Medical college, Gurugram, Haryana, India.
Dr Rashmi Sharma	MD Student, Anaesthesiology and critical care, SGT Medical college, Gurugram, Haryana, India.
Dr Priyanka Dahiya	MD Student, Anaesthesiology and critical care, SGT Medical college, Gurugram, Haryana, India.
Dr Priyanka Kaushik	MD Student, Anaesthesiology and critical care, SGT Medical college, Gurugram, Haryana, India.
Dr Bhavini	MD Student, Anaesthesiology and critical care, SGT Medical college, Gurugram, Haryana, India.

ABSTRACT

Several agents have been described for spinal or epidural anaesthesia adjuvants to facilitate rapid onset of sensory and motor block, and to provide profound perioperative analgesia to ameliorate the surgical stress, and allow early mobility, reducing the need for systemic opioids, decreasing pain scores and works in synergy with other analgesics. In addition, these reduce systemic opioid-related side effects like sedation and can shorten hospital stays and reduces the total cost. Intrathecal (IT) morphine provides long-lasting analgesia for 6-24 hr or even more, but carries significant risk, notably respiratory depression to arrest, pruritus, nausea/vomiting, biphasic blood pressure changes (hypotension/ hypertension) bradycardia, and urinary retention to anuria and seizures to coma and death. These side effects are dose-dependent, with significantly increased risk at doses >300 µg or greater. These side effects are reversed with naloxone (400mcg) bolus or (100-200 mcg/ hr) infusion, a specific opioids (morphine) receptors antagonist. Despite, the primary treatment with intravenous naloxone, severe cases may require mechanical ventilation for respiratory depression and arterial desaturation, and control of hypotension with volume, phenylephrine and norepinephrine, and hypertension with labetalol and hydralazine. Early recognition is critical as toxic overdose may lead to coma or status epilepticus. We present a case of 40 years- female patient, posted for total abdominal hysterectomy(TAH) for abnormal uterine bleeding after obtaining an informed consent, who received inadvertently 3mg morphine in the spinal anaesthesia instead of 100mcg and developed respiratory depression generalized itching, nausea vomiting and over sedation that was refractory to bolus and infusion of naloxone and finally successfully managed with CSF lavage as 50 ml of CSF replaced with 60 ml of normal saline from L3-4 spinal space by removal of morphine from the CSF and diluting the residual drug.

KEYWORDS

Adjuvants, Bupivacaine, CSF lavage, epidural analgesia, intrathecal morphine, neurotoxicity, naloxone, respiratory depression, spinal anaesthesia, toxicity

INTRODUCTION

Now a days, various adjuvants are used with local anesthetics in spinal or epidural anesthesia to improve block quality, rapid onset, and extend the duration of sensory and motor blockade, and allowing for lower doses of local anesthetics, and so reduce the side effects. These work synergistically to enhance anesthesia and improve postoperative pain management. The armamentarium of local anesthetic adjuvants have evolved over time from classical opioids to a wide array of drugs spanning several groups and varying mechanisms of action like opioids (morphine, fentanyl, sufentanil), alpha-2 agonists (clonidine and dexmedetomidine) and steroids(dexamethasone), and others such as magnesium sulphate , ketamine, sodium bicarbonate, neostigmine have also been used with mixed success.[1] Most of these agents are safe and effective to provide the profound intraoperative analgesia, extended to the postoperative period when used in the appropriate doses. However, patients be continuously monitored for the side effects. Among these morphine sulphate has been the most consistent in both spinal and epidural anaesthesia with a dose of 50-300 mcg and 1-5 mg respectively. Its hydrophilic nature enables slow rostral spread with prolonged analgesia, even when delivered at the lumbar level. [2] It provides analgesia without causing sympathetic or motor blockade and so offers targeted pain control for 6 hr to 24 hrs or even more due to its hydrophilic properties. The single most serious adverse event encountered during the administration of intrathecal morphine is respiratory depression or respiratory arrest.[3,4]The respiratory depression due Intrathecal morphine can last up to 24 hours following administration.[5] This respiratory depression follows a biphasic pattern with initial onset within the first 1 to 3 hours and a late-onset at about 6 to 12 hours after administration. Clinicians should limit additional opioids for the first 24 hours after administration. If additional opioids are necessary, the patient should be monitored closely for signs of respiratory depression/apnoea.

Despite the potential for complications such as pruritus, post dural puncture headache, and dose-dependent respiratory depression, spinal opioids remain a valuable tool when appropriately selected and monitored.The complications of the over dose of intrathecal morphine(>300mcg) are usually reversed with bolus or infusion of naloxone, rarely mechanical ventilation is required for the management of respiratory depression and oxygen desaturation and volume and vasopressors for hypotension and antiemetics for nausea and vomiting (ondansetron, dexamethasone, metoclopramide). Sometimes, even infusion of naloxone remains ineffective in reversing the major side effects of intrathecal morphine, in such patients CSF lavage is an effective therapy resulting in fast improvement in respiratory depression and sedation and other sign and symptoms of

morphine toxicity. We have described a CSF lavage as a rescue maneuver for refractory Intrathecal morphine toxicity following total abdominal hysterectomy that was refractory to the bolus and infusion of naloxone.

Case Presentation

A 40 yrs, female, weighing-66 kg presented with abnormal uterine bleeding and endometriosis scheduled to undergo TAH. She was a known case of hypertension for the last 4 years and on regular oral telmisartan (40 mg) plus amlodipine (5mg) daily. Other systems were normal but had persistent vaginal bleeding for 6 months. Spine examination confirmed suitability for combined spinal and epidural anesthesia. In addition, the CVS and respiratory system examination were unremarkable. Her BP was 134/ 84 mmHg, heart rate was 82 bpm, and arterial blood oxygen saturation (SPO2) of 99% 0n room air. Hematological and biochemical values were within normal limits. ECG revealed a T wave inversion in Lead II and V4,5,6 suggestive of infero-lateral myocardial ischemia.[Figure 1] Chest X-ray showed normal lung fields and cardiac shadow.Transthoracic 2-D echocardiography revealed severe concentric left ventricular hypertrophy(LVH), grade - 3 diastolic dysfunction, mild tricuspid regurgitation, and normal LV systolic function with EF of 60%.She was posted for total abdominal hysterectomy after obtaining an informed consent. All cardiac medications were continued on the day of surgery.

In OR, all standard ASA monitors were attached (NIBP, HR, ECG, Spo2, Temperature), and urine output was also monitored via a Foley catheter in view of intrathecal morphine adjuvant and major surgery. Her initial BP was 138/88 and HR was 90bpm, regular and good in volume, without any radio-femoral delay, SPO2 of 98% and intraoperative ECG also revealed the ST/T changes. An 18-gauze IV cannula was inserted in the left upper arm. The team comprising anaesthetist and gynaecologist planned for the combined spinal and epidural anesthesia.

The anesthesia team initially planned to give 3mg morphine in 5 ml saline in epidural space for analgesia and 100 **µg** morphine as adjuvant in spinal anaesthesia with heavy bupivacaine (0.5%, 2ml). The epidural catheter was placed through 18G, Tuohy needle in the L2-3 spinal space and a test dose given using lignocaine with epinephrine 2%, 3 ml. However, 3mg morphine as an adjuvant with 2 mL of 0.5% hyperbaric bupivacaine was inadvertently administered in spinal anaesthesia in L4-5 space via 25 G Quincke,s needle after noting a free CSF flow, due to an error in communication within the anesthesia team. However, the error was identified immediately after the administration of spinal anesthesia. The subsequent procedure followed standard protocols. Initially, a bolus of antiemetics was administered, consisting of metoclopramide (10 mg), cimetidine (200 mg), ondansetron (4 mg), and dexamethasone (8 mg). Intraoperatively, patient developed one episode of hypotension(75/46 mmHg) that was managed with bolus of lactated ringer solution 250 ml and mephenteramine (6 mg). In addition, she started complaining of continuous severe body itching mainly on nose, and sweating, feeling of warmth, sedation with decreased alertness and developed anuria, and respiratory depression, respiratory rate decreased to 10-12 breaths/ min and saturation came down to 86-88% requiring oxygen supplementation to maintain saturation of 98-99%. Her bilateral pupils were pinpoint but reactive to light bilateral. Infusion of LR 500 ml and furosemide 5mg i.v. improved the urine output to approximately 250 ml in one hour. There was a partial improvement in itching with Injection hydrocortisone (100 mg iv), pheniramine 1 amp iv, naloxone 200 mcgs iv bolus. Infusion of NTG (0.5 µg/kgmin) was started in view of diastolic dysfunction, and MI and stopped intraoperatively in view of hypotensive episode. TAH was performed, meticulous hemostasis was achieved, and abdomen was closed. The total duration of the procedure was 165 min, and total blood loss was 600 ml and one unit of PRBC was transfused. Postoperatively, the patient remained sedated, and desaturating (SPO2 -80-85%) without oxygenation and required Hudson mask oxygenation with a flow of 5L/min, that maintained a SPO2 of 98%, but she was drowsy and had a respiratory rate of 9-10 /min and severe itching and anuria. Therefore, it was decided to repeat naloxone 400 µg + 400µg, and ringer lactate 800 ml, and frusemide 10 mg to counter the refractory anuria. There were an intermittent remission and recurrences of the clinical scenario and further flare up postoperatively after 6hrs.

The care team was also put on alert to assess the GCS every 15 min and to monitor for the emergence of nausea, vomiting, or pruritus. An emergency airway trolley was made available and ready for use and instructions for naloxone infusion at a rate of 100 mcg-200 mcg/hr use on the indications of respiratory distress. As the patient had refractory respiratory depression(9-10/min), and continued to be drowsy and complaining of persistent itching, a naloxone infusion(100mcg/hr - 200 µg/hr) was started for 6 hrs. she received a total dose of 2.5 mg of Naloxone. However, there was not much improvement observed in respiratory depression, sedation and itching. Therefore, it was decided to perform the CSF lavage to remove the morphine from the spinal canal CSF and dilute the residual morphine with normal saline. A lumber puncture was performed in L4-L5 space and Isovolumic CSF replacement was done. 50 ml of CSF was exchanged with 60 ml of normal saline; 10 ml extra saline was injected to compensate any CSF leakage post lumber puncture. [Figure 2] Following CSF lavage alertness, itching and respiration improved within 30-40 min. She maintained the hemodynamic (BP 112-153/ 62-93 mmHg), RR around 14-16 breaths per minute and SPO2 of 98-99% with minimum oxygen support (2L) via nasal prongs and remained pain free. The first analgesic was asked by the patient after 42.5 hrs, and for that bupivacaine (0.125%), 5ml was administered for epidural analgesia. The epidural catheter was removed on 3rd postoperative day as patient was completely pain free. Despite all the complications of intrathecal morphine overdose, the patient was absolutely pain free and stress free and that allowed the hemodynamic stability (BP, HR) particularly in the presence of grade -3 diastolic dysfunctions. The patient was shifted to the postoperative ward on 3rd postoperative day, and rest of the course remained uneventful, and she was discharged on the 7th postoperative day.

DISCUSSION

Adjuvants are added to the local anaesthetics(LA) used for spinal(SA) or epidural anaesthesia(EA) to improve the quality, speed of onset, and duration of sensory-motor block while enabling lower, safer doses of the primary anaesthetic and facilitates the early mobility, shorten the length of hospital stay and lower the cost.[1] Recently, α2-agonists(dexmedetomidine (5-10 mcg), clonidine (10-75 mcg) are increasingly being acknowledged as a local anesthetic adjuvant.[6,7,8]

Dexmedetomidine also provides added sedation, reduces shivering, and improved postoperative analgesia. Opioids like fentanyl(10-25 µg), sufentanil (SA-2.5- 5 µg, EA- 0.75-1 µg/mL), morphine(SA-100-300 µg,EA- 1-5 mg) provide strong pain relief.[1] Magnesium(50 mg) provides Sensory / motor block for 366.4□ ±□ 30.12 min / 336.5□±□37.08 min respectively.[9] Dexamethasone (4mg or 8 mg) works By lowering inflammation, preventing nociceptive C-fiber transmission, and inhibiting ectopic neuronal discharge. In addition, dexamethasone reduces pain mediated by preventing the synthesis and release of inflammatory mediators. It provides the mean durations of sensory block for 347.42□ ±□ 91.06 min, and motor block for 308.36□ ±□ 80.91min, and overall analgesia of 421.51□ ±□ 121.62 minutes.[10] Hydromorphone (SA-100 µg and EA- 500-600 µg) preferred in patients with renal insufficiency. Buprenorphine doses for SA are 75-150 µg and EA are 150-300 µg with variable success. Even tramadol has been used as an adjuvant in doses of 10-50 mg in SA, and 1-2 mg/kg in EA with less respiratory depression and successfully used in obstetric patients and abdominal surgeries to pediatric patients for lower abdominal procedures. it is a selective agonist of µ-receptors, also inhibits noradrenaline reuptake and enhances the release of both serotonin and noradrenaline.[11] Even midazolam (1.5-2 mg) is used as an adjuvant and maintain a better intraoperative sedation and moderate prolongation of postoperative analgesia, and vasoconstrictors like epinephrine 2mcg/ml are in use to reduce vascular uptake. Some authors have observed an early onset of sensory and motor block, with longer duration of postoperative effective analgesia with midazolam adjuvant in spinal anaesthesia (243.71 ± 44.95 hours). [12] Ketamine has the significant analgesic properties due to interaction with cholinergic, adrenergic and 5-hydroxy tryptamine systems, and a direct action of ketamine on dorsal horn is also reported. Ketamine can prevent action potential conduction by an effect on sodium and potassium channels in the nerve membranes and hence is considered to have local anaesthetic properties. Ketamine can selectively block the NMDA excitation of central neurons.[13]

As she had grade -3 diastolic dysfunctions, therefore, it is worth highlighting the impact of the diastolic dysfunctions on the IT morphine toxicity and vice versa. Diastolic dysfunction increases a

patient's vulnerability to the adverse cardiovascular effects of intrathecal morphine and magnifies with reduction in HR, SBP/DBP. Intrathecal morphine high doses pose an increased risk of perioperative adverse cardiovascular events in patients with diastolic dysfunction like major adverse cardiac events(MACE),Reduced CO, low cardiac output syndrome(LCOS), AF,myocardial ischemia,Increases mortality, and pprolonged mechanical ventilation as a result of decreased coronary perfusion pressure due to hypotension and bradycardia.[14] The IT morphine, particularly in higher doses, can cause hypotension and, bradycardia, which can be detrimental in reduced diastolic compliance that rely on precise timing and pressure for filling.[14]

Morphine has been extensively used as an adjuvant or sole agent for spinal or epidural analgesia, while highly effective for pain management, also carries a risk of significant side effects and potential for high doses errors as reported by various case reports.[15,16] The hydrophilic nature of neuraxial morphine results in slow cephalad spread, thereby increasing the area of analgesia for 8-24 hours or more. It remains concentrated at the dorsal horn of the spinal cord due to slower uptake, providing more sustained spinal-level analgesia.[5,17] In contrast, intrathecal fentanyl (10–20 μg) and sufentanil (2.5–5 μg) are favored for intraoperative analgesia as their lipophilic properties provides a rapid onset with in 5 to 20 minutes, with a durations of 1 to 4 hours for fentanyl and 2 to 6 hours for sufentanil. In addition, much of their analgesic effects come from systemic absorption and central action in the brainstem, where sedation and respiratory depression may occur.[18] Morphine stimulates opioid receptors in the substantia gelatinosa of the posterior spinal. However, the accidental high-dose intrathecal morphine induces the adverse effect varies from mild problems to very severe complications such as respiratory depression (early and late), nausea, vomiting, pruritus and urinary retention, hyperalgesia, double vision, nystagmus, myoclonus, somnolence, bradycardia, biphasic blood pressure changes(hypotension/ hypertension), respiratory depression with bradypnea and decreased arterial oxygen saturation, sedation to deep coma or seizures due to direct neurone toxicity or with increased 5HT levels or even death.[16,19] These adverse effects may prolong postanaesthesia care unit (PACU) length of stay, unplanned hospital admission, and increase healthcare expenses, along with patient dissatisfaction.[20] Two previous meta-analyses demonstrated that morphine 100 μg was a threshold dose for PONV after Caesarean delivery and lower limb arthroplasty.[21,22] Specifically, there is evidence to suggest that intrathecal morphine administration of doses lower than 100 μg results in lesser adverse effects particularly in elderly patients.[23]

Generalized itching though mild, but appears particularly around the nose on the face is the most common side effect. It is usually treated effectively with specific medications like low-dose naloxone 400mcg bolus or ondansetron(4mg). Naloxone is the antidote for IT morphine side effects, is a competitive mu-opioid–receptor antagonist that reverses all signs of opioid intoxication. The largest reported overdose involved a 510 mg (in 35 mL) bolus of morphine, far surpassing the typical doses used in clinical settings. This case was further complicated by status epilepticus in addition to the anticipated adverse effects.[16] Nausea and vomiting are also significantly high and Prophylactic or rescue antiemetics such as metoclopramide (10 mg), cimetidine (200 mg), ondansetron (4 mg), and dexamethasone (8 mg) are often used for the management.[24] Extreme overdose scenario often results from pump errors or erroneous refills have been associated with rapid onset of hypertension, seizures, and subsequent cerebral bleeding and respiratory depression and even mortality.[25] Respiratory depression is a rare but potentially severe and life-threatening complication and usually accompanies with deep sedation. Both rate and depth of respiration decrease leading to hypercapnia and hypoxemia. Due to morphine's hydrophilic nature rostral migration from the CSF of spinal canal is slow and respiratory depression can be delayed, sometimes occurring 6 to 24 hours or more after administration, which necessitates a period of close patient monitoring. Usually managed with naloxone boluses (0.04 mg iv), or a continuous (100-200mcg/hr) infusion for 12-24 hrs. The initial dose of naloxone is 400μg, which can be increased every 2 minutes to a maximum of 15 mg. The onset of action of intravenous naloxone is generally less than 2 minutes and the duration of action is 20 to 90 minutes, which is much shorter than the IT morphine (6-24 hr), often rendering redosing or infusion necessary.[3,24,26] Hypertension may occur due to increased sympathoadrenal outflow caused by centralized opioid effects, resulting in high levels of plasma catecholamines, or Central Nervous System (CNS) Hypoxia/Stress as a result of Severe respiratory depression leading to hypercarbia and brain hypoxia that can trigger a hypertensive response, and sometimes concomitant myoclonic seizures.it is crucial to manage hypertension with labetalol, NTG, sodium nitroprusside or hydralazine. Some patients may develop even hypotension and require intravenous fluid volume, phenylephrine, norepinephrine or vasopressin to restore the appropriate MAP of >65 mmHg. Status epilepticus is also anticipated in severe intrathecal morphine toxicity with large doses and patinets require therapy with thiopentone, midazolam, propofol,or even ketamine for refractory status epilepticus.[16] Some patients may develop anuria in morphine toxicity because of tubular necrosis due to hypotension, hypovolemia, rhabdomyolysis or triggered by increased ADH release. This patient also developed anuria but responded to the administration of ringer lactate 500 ml and frusemide (5mg) and naloxone infusion (100 mcg/hr).

Management of intrathecal morphine toxicity should focus on prevention or reversing the arterial desaturation due to respiratory depression and preventing seizures and hypertension and hypotension through early administration of intravenous naloxone and supportive care as oxygenation with a mask or nasal prongs, and mechanical ventilation with endotracheal intubation is necessary for significant respiratory depression when naloxone remains ineffective. The mechanical respiration may be required even up to 24 hours. Our patient was responding for 5-10min to the 400mcg boluses, however the episodes of remission and reoccurrence of sedation and respiratory depression were continued despite the naloxone intravenous infusion of 200mcg/hr for 6hrs. Critical measures as a cerebrospinal fluid (CSF) drainage/irrigation have been utilized in severe IT morphine toxicity refractory to the supportive measures and naloxone therapy. Groudine and colleagues, have described a 250 mg IT morphine overdose in a patient chronically exposed to this drug, suggested that attempts to remove as much drug as possible from the cerebro-spinal fluid by aspiration and, if necessary, irrigation should be started immediately. This may avoid direct neurotoxicity of morphine that seems to be responsible for myoclonus unresponsive to i.v. naloxone[15] some authors have suggested that Naloxone should be administered early, as soon as the overdose is discovered and before symptoms appear, and as a continuously infusion at small doses to prevent the adverse effects of naloxone rapid loading dose as rapid increase in sympathetic tone, such as potentially life-threatening hypertension that can lead to hemorrhagic strokes, pulmonary edema, cardiac rhythm disturbances, and re-emergence of pain.

A lumbar catheter (e.g., spinal drain) should be placed immediately to remove morphine-containing CSF and irrigate with normal saline or ringer lactate solution, which significantly lowers the drug concentration and rapid improvement in the morphine toxicity including respiratory depression or weaning from mechanical ventilation, profound sedation, nausea vomiting and itching.[25,27,28,29] WE have inserted a 23 G spinal needle in the lumber region and removed 10 cc of CSF replaced with 10 ml of normal saline at a time, a total CSF (50 ml) and exchanged with 60 ml of normal saline over the 10 min. This approach was well tolerated by the patient, and it facilitated rapid reversal of intrathecal morphine toxicity (alertness and respiratory depression, RR and saturation, pruritic, nausea and vomiting) and allowed discontinuation of naloxone infusion.

CONCLUSION

Inadvertently, intrathecal overdose of morphine adjuvant has been reported in various case reports. The proper communication among the all the team members is essential to minimize the risk of inadvertently intrathecal morphine overdoses. Early detection through awareness and vigilant monitoring can prevent serious complications. Close monitoring of the patient's respiratory status and level of sedation is essential. Over sedation and respiratory depression unresponsive to intravenous bolus and infusion of naloxone may necessitates the CSF lavage in L3-4 interspace and isovolumic saline exchange to remove the morphine from the spinal canal and dilute the residual morphine in the CSF. This process is safe and significantly effective in ameliorating the complications of intrathecal morphine over dose including respiratory depression and deep sedation within 30-40 min of the CSF lavage. The timely CSF lavage can avoid even the requirement of mechanical ventilation as it improves the not only the depth of respiration but respiratory rate also.

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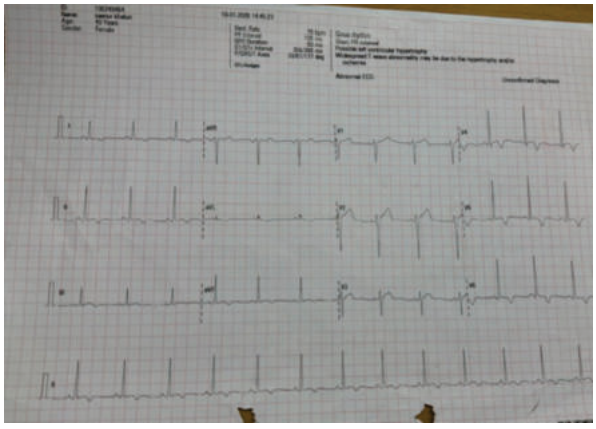

Figure. 1. 12 lead ECG shows T wave inversion in lead -2 and V4, V5, V6 suggestive of Infero-lateral MI and LVH.
MI- myocardial ischemia, LVH- left ventricular hypertrophy

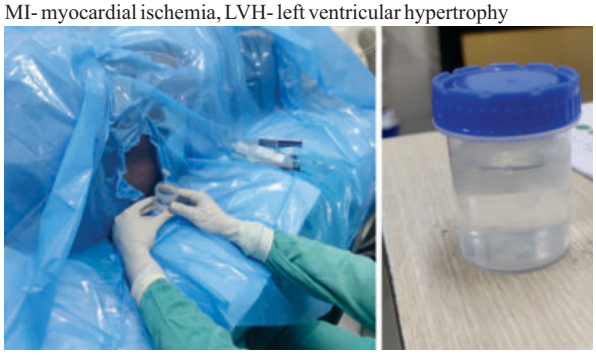

Figure.2. The photograph depicting the process of CSF lavage from the lumber region under strict aseptic process and a container with 50 cc of clear CSF. The 50 cc of CSF was exchanged with 60 ml of normal saline to dilute the residual morphine in the spinal CSF and extra 10 ml saline was administered to counter any CSF leak from the spinal needle puncture.

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