Anesthetic management and perioperative outcome of infants with Biliary atresia: A retrospective review of 40 cases from a tertiary care pediatric institute in India

Anuradha Ganigara[1], Chandrika Y Ramavakoda[2], Bindu[3], Bhargavi Sanket[4], Vinay Jadhav[5], Jayalaxmi Sripathi Aihole[6]

[1,2,3,4]Department of Anaesthesiolgy, [5,6]Department of Paediatric Surgery,
Indira Gandhi Institute of Child Health, Bangalore, Karnataka, India.

***Corresponding Author**:
E-mail: anuradhasudhir@gmail.com

Brief Questions

a. What is already known – Medical literature about Biliary Atresia and anesthetic implications is present but is insufficient and incomplete.
b. What the article adds- The article tries to provide an expatiating review about the disease process with in depth anesthetic implications and its relevance to practicing pediatric anesthesiologists who encounter infants with this disease occasionally.
c. Implications for translation – The article provides a definite impetus for studies relating to non invasive cardiac output monitoring in infants and metabolic and pathophysiological sequel of end stage liver disease in infants.

Abstract

Background: Biliary atresia (BA) is a progressive and fatal obliterative cholangiopathy affecting 1 in 10,000 infants resulting in biliary cirrhosis and eventually death within the first two years of life. The first line of treatment is a surgical procedure known as Kasai's portoenterostomy which aims to restore the forward flow of bile into the intestines. There is paucity of literature regarding perioperative anesthetic management of BA and its outcome. This review was thus specifically done to fill in the dearth with regard to anesthetic challenges and complications met during management of infants with BA undergoing Kasai's procedure.

Materials and methods: Retrospective data of all infants diagnosed and operated for EHBA in our institute from 2011 to 2014 was collected. Perioperative data, anesthetic and surgical details including post operative course of these children were collected and analyzed.

Results: The highlights of our series were the delayed presentation of infants with BA at an average age of 85 days which indirectly prolonged the operative time. These infants in early stages of cirrhosis had higher requirements of crystalloid and blood component therapy. Intraoperatively, a decrease in blood pressure was also reflected in the R wave amplitude of ECG which signals further research in the direction of non invasive hemodynamic monitoring in infants. Of significance was the finding of normal intraoperative blood glucose values in infants with EHBA and thus inadvertent dextrose supplementation in all infants with liver dysfunction needs to be avoided. Multimodal analgesia in the form of intravenous opioids, paracetamol, tramadol and judicious local anesthetic infiltration can be used to tackle perioperative pain.

Conclusions: In conclusion, when faced with anesthetizing infants with EHBA, the anesthesiologist needs to pay attention to the preoperative assessment like age of presentation, severity of the liver dysfunction and associated congenital and co morbid conditions like anemia and coagulopathy. Goals of anesthetic management would include meticulous maintenance of euvolemia, euthermia, euglycemia and provision of adequate perioperative analgesia and anesthesia.

Keywords: Infants, Biliary atresia, Anesthesia, Perioperative care, Outcome, Implications

Access this article online	
Quick Response Code:	**Website:** www.innovativepublication.com
	DOI: 10.5958/2394-4994.2016.00014.7

Introduction

Biliary atresia (BA) is a rare, progressive inflammatory disorder affecting the biliary tree resulting in total obstruction and eventually destruction of both intra and extra hepatic bile ducts in the neonatal period. Without medical intervention, death within the first two years of life is the natural course of disease secondary to cholestasis, fibrosis and biliary cirrhosis which leads to hepatic failure.[1]

The disease can be classified into three types based on the extent of biliary tract involvement.[2] Type I atresia affects the common bile duct and proximal part of cystic duct. Type II involves the common hepatic duct and type III, which is the most common affects the entire extra hepatic biliary tree. Based on clinical presentation, two forms have been identified. The syndromic or embryonic type is associated with other malformations like situs inversus, polyspleenia, cardiac abnormalities. The acquired form is more common and

accounts for 80-90 % of cases. The underlying cause for biliary atresia probably is multifactorial including defects in morphogenesis, immunological dysregulation, viral infection and probable exposure to environmental toxins.[3]

Effective treatment modalities include excision of the affected atretic biliary tree with adequate restoration of bile flow by creation of portoenterostomy popularized by Morio Kasai first performed in 1959, which ensures surgical drainage of bile from liver to intestines.[4] Adjuvant medical therapy and nutritional support is also initiated. Infants with failed portoenterostomy require liver transplantation as the last resort.[5]

In our institute, Kasai's portoenterostomy (KPE) for BA is being performed for the last ten years and a total of 40 children were operated for KPE between 2011 and 2014. Retrospective data of these children was collected to evaluate the perioperative anesthetic management, anesthetic technique employed and postoperative outcome in infants with BA.

Materials and methods

Ethical clearance from our hospital's Institutional Review Board was obtained; case files of 40 infants who underwent KPE for BA were reviewed.

Preanesthetic details including age of presentation, age at time of surgery, birth weight, gender, associated anomalies and preoperative laboratory investigations and other relevant data were assessed.

Anesthetic chart details mentioning the anesthetic technique, drugs employed fluid and blood transfusion data, serial blood glucose values were noted.

Postoperatively, episodes of cholangitis, hepatic decompensation and final outcome of KPE were evaluated. KPE was successful if the child had direct bilirubin levels less than 2 gm/dl at six months post surgery. Mean follow up period of our patients was for 20 months.

All infants with a clinical diagnosis of EHBA were sent for pre anesthetic evaluation 1 week prior to surgery. Uniform medical optimization of these infants included administration of oral ursodeoxycholic acid and supplementation of multivitamins including vitamin K.

Preoperatively, on the day of surgery fasting orders for 4 hours to breast milk was issued with arrangements made for postoperative surgical intensive unit care bed facility and availability of adequate compatible blood components for intraoperative use.

In the operating room, necessary monitoring devices (Electrocardiography, Non invasive blood pressure cuff, Pulse oximeter) are attached to the infants before induction. A minimum of two 22 Gauge intravenous lines are secured in the upper limbs after induction with sevoflurane in air oxygen mixture with inspired oxygen concentration of 0.4. In all infants with intravenous lines, induction proceeded with injection of Thiopentone sodium 5mg/kg and injection Morphine sulphate 0.01 mg/kg with atracurium bresylate 0.5 mg/kg to facilitate tracheal intubation.

Controlled mechanical ventilation with oxygen in air and isoflurane 1 % was delivered to ensure normocapnia. Neuromuscular blockade was maintained with infusion of atracurium at 0.5 mg/kg/ hour which was switched off approximately forty five minutes before closure. Additional analgesics supplemented were both intravenous fentanyl (1ug/kg) and paracetamol (10mg/kg) in intravenous formulation or suppository route. Ringer's lactate was uniformly used as crystalloid of choice and packed red blood cells were administered when the loss exceeded maximal allowable blood loss.

Intraoperatively the heart rate, electrocardiograph, plethysmography, non invasive blood pressure, end tidal carbon-di-oxide gas levels, nasopharyngeal temperature, urine output and blood glucose levels were monitored. At the conclusion of surgery, neuromuscular block was reversed with injection neostigmine 0.05mg/kg and glycopyrollate 0.01 mg/kg and the infant was extubated and shifted to surgical intensive care unit.

Bolus doses of intravenous tramadol 1mg/kg eight hourly and paracetamol 10 mg/kg eighth hourly for 48 hours were used for postoperative analgesia.

Post discharge surgical orders included oral prednisolone 1mg/kg for three months and antibiotics to prevent cholangitis. Oral ursodeoxycholic acid to encourage bile flow and supplemental nutritional therapy to overcome fat malabsorption and excess catabolic stress.

Post discharge follow up was after 3 weeks or earlier if the child had any symptoms of cholangitis and subsequently every 6 months later on.

Results

Anesthetic and surgical record data of 40 infants operated for KPE was analyzed and is presented below. Demographic data of the 40 infants is depicted in Table 1. Twenty four males and sixteen female babies were operated for KPE in the last 3 years. The mean age and weight of infants presenting for KPE was 85 days and 4.5 kilograms.

The most common symptom of presentation was passage of clay colored stools, high colored urine and progressively deepening jaundice since birth. Nine infants presented with late symptoms and are described in Table 2.

Table 1: Demographic Data

DATA	MEAN	RANGE
AGE AT SURGERY	85 days	23-180 days
WEIGHT	4.5 kilograms	2.8- 7 kilograms
SEX M:F	24 : 16	
HEPATOMEGALY	39/40 (9.5-3CM)	
SPLEENOMEGALY	27/40 (8- 1 CM)	
CONGENITAL HEART DISEASE	7/40	1 patient had situs inversus
HIDA scan	Positive 40/40	
USG	Triangular cord sign documented in 33/40 patients (2mm-6.6mm)	
LIVER BIOPSY SCORING	Documented in 31/40 patients. CFS reported IN 27/31(1-6) Largest duct size reported in 23/31 (600- 8 um)	

Seven infants were diagnosed with uncorrected congenital heart disease preoperatively, four of them had ostium secondum type atrial septal defect, largest being 7 mm with dilatation of right chambers of the heart. One infant had associated apical ventricular septal defect. Two infants had patent foramen ovale with patent ductus arteriosus. One infant was diagnosed with situs inversus with dextrocardia. All the above seven infants had good biventricular function with no cardiorespiratory compromise.

Hepatomegaly was present in all the infants and twenty seven of them had associated splenomegaly with splenic size ranging from 8 centimeters to 1 centimeter below the left costal margin.

Preoperatively HIDA scan was highly suggestive of EHBA in all patients with the Triangular cord sign being positive in thirty three patients.

Table 2: Details of Infants with Symtoms of Late Presentation

Sl.No	Age-days	Sex	Weight-kg	DESCRIPTION
1	60	M	4.8	Child presented with epistaxis with coagulopathy, PT- 96 seconds, APTT- 175 seconds. Managed with Vitamin K and FFP administration.
2	150	M	4	Associated history of noisy breathing since birth, bronchoscopy confirmed tracheomalacia with bulky epiglottis and in drawing of anterior commissure.
3	60	F	4	Associated sepsis with coagulopathy, PT, APTT >300 seconds
4	45	M	4	Associated sepsis with coagulopathy, anemia
5	60	F	3.8	Child presented with altered sensorium, vomiting and seizures- ultrasound revealed intracranial hemorrhage
6	60	F	4.3	Child presented with ecchymotic patches with coagulopathy
7	90	M	4	Child presented with poor weight gain, diagnosed as Failure to thrive baby
8	30	M	2.8	Child presented with right septic arthritis of hip with psoas abscess. Postoperatively diagnosed to have malrotation and operated subsequently.
9	90	F	4.2	Child presented with hematoma over left cheek, PT, APTT > 3 minutes

Preoperative laboratory data with liver function tests is depicted in Table 3. Six infants required preoperative packed red blood cells (PRBC's) to treat co existing anemia less than 8 gm/dl. Three of them received fresh frozen plasma (FFP) to correct underlying coagulopathy and two infants required transfusion of both packed cells and plasma. Liver enzymes were elevated in all the patients as mentioned in the table. The mean albumin value was 3.37gm/dl.

Table 3: Liver Biochemistry Reports

DATA	MEAN	Documented RANGE
Bilirubin mg/dl	13.635	28- 6.7
Conjugated Bilirubin mg/dl	8.5725	18.1- 3.6
Aspartate transferase U/L (SGOT)	401	1182-66
Alanine transferase U/L (SGPT)	266	1000-35
Alkaline phosphatase U/L	832.8	5620- 172..3
Albumin mg/dl	3.37	4.1-2-5
Platelets cells/cumm	2,97,000	7,16,000 - 1,02,000
Prothrombin time seconds	16.786	33- 13.2
Activated partial thromboplastin time seconds	42.584	80- 27
Hemoglobin (gm/dl)	9.98	16.4- 6.2
Preoperative PRBC transfusion	8/40	15ml/kg
Preoperative FFP transfusion	5/40	15ml/kg

The surgical procedure lasted on an average of 267 minutes. An average of 63 ml/kg ofRinger's lactate was infused during the surgical procedure with mean blood loss of 12.5ml/kg which in total amounted to 15.625% of blood volume lost.

Intraoperatively 55 % of children required packed red blood cells transfusion with 77.5 % requiring fresh frozen plasma. 5% of infants received both plasma and packed cells. Average PRBC transfused was 50.68 ml, approximately 11ml/kg and average FFP transfused was 63 ml amounting to 14 ml/kg.

Blood glucose was measured initially and again at two hours interval in 22 patients. 101mg/dl was the average glucose level after induction and the second hourly glucose averaged to 184.31 mg/dl. All patients received intravenous morphine and surgical skin incision was infiltrated with 0.2% Bupivacaine. Paracetamol was administered either as an intravenous infusion at 10mg/kg over ten minutes or as suppository of 40mg/kg before surgical incision. Supplemental intravenous fentanyl was injected in five patients.

Two infants had transient bradycardia with heart rates less than… SD for their age group with concomitant drop in blood pressure of >20 %. Four infants had delayed recovery due to hypothermia, despite measures taken to maintain normothermia. One of them required post operative mechanical ventilation for 24 hours in view of severe hypothermia with the lowest temperature recorded at 32.8C.

Table 4: Perioperative Data

DATA	MEAN	RANGE
Duration of surgery hours	267 minutes	190- 420 minutes
Ringer Lactate infusion ml	284	500- 150
Blood loss ml	56.25	(170-10)
Packed red blood cell infusion ml	(22/40) 50.68	100-20
Fresh frozen plasma infusion ml	(31/40) 63.06	120-20
Glucose mg/dl	101.63	155-64

Postoperatively, one child died on the first postoperative day 17 hours after surgery due to massive pulmonary hemorrhage. Twelve children among the 40 did not come for follow up after initial discharge. Seventeen of them expired post procedure within a span of 1 month to 1 year post surgery. Ten of them are alive and doing well with no jaundice. Average incidence of cholangitis in the surviving group was 2 episodes during the follow period.

Discussion

Kasai's portoenterostomy is still the first and often the only hope for survival in infants presenting with biliary atresia in developing nations. Pediatric anesthesiologists managing these jaundiced infants are often caught walking on a tight rope to maximally optimize them and give the infants their best chance for survival perioperatively.

Important anesthetic concerns would include maintenance of euvolemia, euthermia, euglycemia and provision of adequate perioperative analgesia and anesthesia.[6] This retrospective review article aims to put forth the various perioperative considerations in neonates with cholestasis and anesthetic management of infants with hyperbiliru-binemia. The perioperative complications encountered and long term outcomes of these infants with BA from a single centre in India are discussed in this review.

Anesthesia for infants with BA necessitates an understanding of neonatal cholestasis and its subsequent effects on various organ systems. Neonates with BA typically present with persistent jaundice, pale stools and dark urine. As the conjugated bilirubin cannot enter the intestines, the stools remain acholic and the excess conjugated bilirubin remains in the blood stream causing progressively deepening jaundice. The excess water soluble bilirubin is excreted in the urine giving it its characteristic color. These infants in the early stages appear misleadingly healthy when they present for KPE. If the early signs go unnoticed, gradually liver failure sets in with signs of, failure to thrive due to impaired absorption of long chain fatty acids, vitamin K responsive coagulopathy, hepatosplenomegaly and ascites which suggest cirrhosis.[7] The synthetic function of the liver is usually well preserved until the late stages of the disease.[8]

A baseline albumin, glucose, prothrombin time and its international normalized ratio are needed to know the severity of liver dysfunction. Coagulopathy unresponsive to vitamin K administration suggests either failure of liver's synthetic function, undernutrition or sepsis.

In our institute, 67 % of the infants had spleenomegaly and 20 % had associated coagulopathy on initial presentation. The average age of neonates when presented for KPE was 85 days which explains the presence of early signs of cirrhosis in our cohort of patients.

Though the King's college series has documented that there is no real cut off mark (60-80 days) beyond which KPE is unlikely to be successful, the fibrotic changes induced by BA would be in progress and would eventually result in liver damage.[9]

Thus, later the age of presentation, these neonates are likely to be more sick which would mandate medical optimization before surgery crucial.

More than 20 % of infants with BA have associated congenital anatomical malformations of which presence of congenital heart disease (CHD) is of relevance to the anesthesiologist. Cardiac anomalies - ventricular septal defect, atrial septal defect, patent foramen ovale, hypoplastic left heart are commonly encountered.[10] In our series 7 infants had associated simple uncorrected congenital heart disease. Infants with BA with even simple CHD should be prioritized as high risk category undergoing non cardiac surgery. Reasons include anticipated systemic hypotension owing to blood loss/surgical maneuvers in an already tipped cardiovascular physiology, major intraperitoneal surgery causing fluid shifts with dramatic in vivo changes in temperature further affecting the deranged body mechanisms.

Our next concern was the duration of procedure and critical surgical maneuvers which cause anticipated hemodynamic instability. Hypothermia and fluid therapy were significant challenges in our series with the average duration of surgery lasting for 267 minutes. By placement of warming blankets, protective plastic sheets covering the entire body, infusing warm intravenous fluids and using warm irrigation fluids we ensured euthermia.

The critical surgical event during KPE is exteriorization of liver from abdominal cavity to explore the porta hepatis which results in drop in blood pressure due to kinking of inferior vena cava and subsequent obstruction of venous return.[11] This drop in blood pressure was seen in most patients and responded to simple fluid boluses of 5-10 ml/kg. Alternatively, a fluid bolus before exteriorization of liver also avoided the drop in blood pressure. In four cases this drop in blood pressure was reflected on the R wave amplitude of ECG which has been described as Brody's effect. The concomitant reduction in R wave amplitude of the ECG has been attributed to reduction in ventricular blood volume.[12]

Two infants had transient bradycardia which was probably a vagal response to liver traction was documented. Releasing the traction and administration of glycopyrollate were the measures taken to treat bradycardia. John P and colleagues have reported similar case of intense vagal stimulation causing bradycardia and asystole in a patient undergoing hepatectomy.[13]

While anesthetizing these infants the anesthetic technique employed should result in least perturbation of the fragile hepatobiliary function with optimal hepatic artery blood flow maintained throughout the surgical period.[14] Anesthetic agents with minimal hepatotoxic effects need to be administered to avoid further deterioration of liver function. Isoflurane is the inhalational agent of choice because of its ability to increase the arterial hepatic blood flow with minimal decrease in total hepatic blood flow.[15]

Sevoflurane, also has been safely used for inhalational induction as it is devoid of any hepatotoxic effects.[15] The effects of intravenous anesthetic agents

are influenced by hepatic artery blood flow, presence of portosystemic shunts, decreased hepatic enzyme activity and alteration in plasma protein binding.[16] Atracurium was used as the neuromuscular blocker of choice as its metabolism is independent of liver function.[17]

Morphine (0.1mg/kg) was used for intraoperative analgesia in our group of patients. The hepatic synthetic and metabolic functions are relatively unimpaired till late stages, thus doses of opioid analgesics remain unchanged. [6]

Adjuvant analgesics used were intravenous bolus doses of fentanyl, paracetamol 10mg/kg with 0.25% bupivacaine wound infiltration at end of procedure and postoperative use of tramadol in doses of 1mg/kg 12th hourly. Pharmacokinetics of tramadol in neonates and young infants have been studied by Allegaert at al who found the maturation of clearance of tramadol is almost complete by 44 weeks of post conceptional age.[18] In children with mild to moderate Child Pugh scoring tramadol can be used but the dose needs to be halved and the dosing interval increased from 6 hours to 12 hours.[19] Nitrous oxide is generally avoided to prevent gut distension hampering abdominal closure at the end of procedure. Regional anesthesia in these infants was avoided taking into consideration the abdominal distension and possible perioperative coagulopathy.

Care should be taken to avoid high airway pressures and hypocarbia as both can reduce hepatic and portal blood flow, thus controlled ventilation to maintain normocarbia should be ensured.[21]

Perioperative fluid management needs to be titrated to maintain euvolemia. In our series, an average of 63ml/kg of Ringer's lactate was infused intraoperatively when compared to 25ml/kg in the King's series probably due to doubling of surgical time. Average blood loss amounted to 15.6% was replaced in 55 % of patients. Fresh frozen plasma was transfused in 77.5% of patients which reflects its use as a probable alternative to colloid which is mostly unavailable in our setting. Also, the plasma was mostly used in cases where perioperative coagulopathy was suspected by the attending anesthesiologist.

Average blood glucose level was 101.63 mg/dl soon after induction in our series of patients. Glucose containing crystalloid solutions was infused only if hypoglycemia was documented. 1% Dextrose in Ringer lactate solution to counter hypoglycemia was used in one infant. The second hour blood glucose averaged at 184.31 mg/dl. Thus, though hypoglycemia is a real concern, unless documented dextrose solutions need to be used prudently.

Thus, the highlights of our series were the delayed presentation of infants with BA at an average age of 85 days which indirectly prolonged the operative time. These infants in early stages of cirrhosis had higher requirements of crystalloid and blood component therapy. Intraoperatively, a decrease in blood pressure was also reflected in the R wave amplitude of ECG which signals further research in the direction of non invasive hemodynamic monitoring in infants. Of significance was the finding of normal intraoperative blood glucose values in infants with BA and thus avoiding inadvertent dextrose supplementation in all infants with liver dysfunction. Multimodal analgesia in the form of intravenous opioids, paracetamol, tramadol and judicious local anesthetic infiltration can be used to tackle perioperative pain.

Limitations of the present study are its retrospective nature with a few observations regarding perioperative management being missed out in the anesthesia charts. In addition, the number of children lost to follow up could have resulted in skewed survival ratio.

In conclusion, when faced with anesthetizing infants with EHBA, the anesthesiologist needs to pay attention to the preoperative assessment like age of presentation, severity of the liver dysfunction and associated congenital and co morbid conditions like anemia and coagulopathy. Goals of anesthetic management would include meticulous maintenance of euvolemia, euthermia, euglycemia and provision of adequate perioperative analgesia and anesthesia.

Disclosures

Ethical Clearance: No deviation from standard care of treatment
Source of Grants: NONE
Conflict of Interest: No conflict of interest declared

References

1. Hartley J L, Davenport M, Kelly D A. Biliary atresia. Lancet 2009;374:1704-13
2. Kelly D A, Davenport M. Current management of biliary atresia. Arch Dis Child 2007;92:1132-35.
3. Wildhaber B E. Biliary atresia: 50 years after first Kasai. ISRN Surgery 2012,Article ID 132089. Doi : 10.5402/2012/132089.
4. Davenport M. Biliary atresia: outcome and management. Indian J Pediatr 2006; 73:825-8
5. Kasai M and Suzuki S. A new operation for non corrective biliary atresia: hepatic portoenterostomy. Shuiyutsu 1959; 13:733-39.
6. Green D W, Howard E R and Davenport M. Anesthesia, perioperative and outcome of correction of extrahepatic biliary atresia in the infant: a review of 50 cases in the Kings's college hospital series. Paediatr Anaesth 2000;10:581-89
7. Sokol R J, Mack C, Narkewicz M R, Karrer F M. Pathogenesis and outcome of biliary atresia: current concepts. J Pediatr Gastroenterol Nutr 2003;37:4-21
8. Bates M D, Bucuvalas J C, Alonso M H, Ryckman F C. Biliary atresia: pathogenesis and treatment. Semin Liver Dis 1998;18(3):281-93
9. Davenport M, Caponcelli E, Livesey E, Hadzic N, Howard E. Surgical outcome in biliary atresia: etiology affects the influence of age at surgery. Ann Surg 2008;247:694-98
10. Davenport M, Tizzard S A, Underhill J, Mieli-Vergani G, Portmann B, Hadzic N. The biliary atresia splenic

malformation syndrome: a 28 year single centre retrospective study. J Pediatr 2006;149:393-400
11. Elsadat A M. Biliary atresia: Experience with 30 consecutive cases in a single institute. Annals of Pediatric Surgery 2009;5:233-40
12. Ganigara A, Ramavakoda C Y. Clinical evidence of Brody's effect in infants undergoing Kasai's portoenterostomy for biliary atresia. Paediatr Anaesth 2014;14:1193-94
13. John P, Raj S, Kartikeyan, Chandy T T. Asystole following profound vagal stimulation during hepatectomy. Indian J. Anaesth 2008;52(1) :81-82
14. Muller G and et al. Anesthetic considerations in progressive familial intrahepatic cholestasis (Byler's disease). Can J Anesth 1995;42(12):1126-33
15. Hammer G, Hall S, Davis P J. Anesthesia for general abdominal, thoracic, urologic and bariatric surgery. In : Motoyama E K, Davis P J,Cladis F P. Smith's anesthesia for infants and children.8th ed, Mosby Elsevier Publ. 2011.
16. Gatecel C, Losser M R, Payen D. The post operative effects of halothane versus isoflurane on hepatic artery and portal vein blood flow in humans. Anesth Analg 2003;96(3):740-45.
17. Steadman R H. Anesthesia for liver transplant surgery. Anesthesiology Clin N Am 2004;22:687-711.
18. Allegaert K and et al. Tramadol disposition in the very young: an attempt to asses in vivo cytochrome P-450 2D6 activity. Br J Anaesth 2005;95(2):231-39.
19. Davis M P, Glare P A, Hardy J, Quigley C. Opioids in cancer pain. 2nd ed, OUP Oxford 2009.