

# Failure of Immediate Tracheal Extubation After Liver Transplantation - A Single Center Experience

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**Abstract:** Fast tracking approaches in liver transplantation include postoperative extubation immediately after surgery in the operating theatre. Based on the experience of 837 liver transplantations performed between 01/97 and 05/05, we report on the safety and feasibility of this procedure in almost 80% of transplant recipients, without increasing the incidence of subsequent reintubation (11%). This patient population experienced significantly higher survival compared to patients in whom extubation succeeded at the intensive care unit ( $p < 0.02$ ). Special attention was required for recipients with acute liver failure or retransplantation. These patients did not participate in fast tracking protocols, as demonstrated by a multivariate regression analysis. In this context, failure of immediate tracheal extubation was independent of cold ischemic time, duration of surgery, donor / recipient age or gender, extent of preservation injury, or type of organ donation (post-mortal vs living-related). ROC analysis revealed that only intraoperative transfusions of  $\leq 6$  units of red blood cells were associated with primary extubation in the operating theatre with high sensitivity and specificity. To conclude, postoperative mechanical ventilation is justified only in a small cohort of recipients. For the vast majority of  $\leq$  patients, immediate postoperative tracheal extubation should be the standard procedure after liver transplantation.

**Keywords:** Liver transplantation, tracheal extubation, reintubation.

## INTRODUCTION

Orthotopic liver transplantation (LTX) is an established therapy for acute liver failure, advanced liver cirrhosis and liver tumors [1]. Despite the complexity of this intervention, it, due to numerous anesthesiological and surgical improvements, increases the survival rate of up to 90% during the first year after transplantation [2].

In many transplant centers perioperative approaches are carried out according to the standardized procedure, however, new concepts must constantly be incorporated to keep up with the pathophysiological procedures of a transplantation. An important innovation is the so-called "fast tracking" concept, which, instead of lengthy controlled mechanical ventilation, enables a premature withdrawal of the respirator [3].

Due to the acquired knowledge of the interaction of artificial ventilation and hepatic blood flow, ventilation time on intensive care unit could be decreased tremendously and early postoperative extubation was well established [4-9]. The advantages of this are the distinct improvement of preservation damage of the perfused liver graft, thus enabling an efficient recovery of the donor liver [3, 10]. It is however undisputed whether the preservation damage and the thereon dependent postoperative graft function have a direct influence on the subsequent course of recovery [11]. Consequently, in numerous transplant centers the extubation time-

point now takes place in the operating theatre, without increasing the reintubation rate [12-14].

However, in spite of all these advantages not all patients profit from the fast tracking concept. The rate of extubation in the operating theatre is currently approximately 80%, which implies that still about one fifth of all patients in intensive care unit receive artificial ventilation [5, 8, 12, 14-16].

In our retrospective analysis we tried to find out which factors are responsible for preventing primary extubation after liver transplantation in the operating theatre.

## PATIENTS AND METHODS

A total of 873 out of 879 orthotopic liver transplantations performed between 01/97 and 05/05 was included in our retrospective analysis (exclusion criteria: recipient age  $< 14$  years). For the statistical analysis patients were divided into two groups and categorized according to their postoperative time of extubation (Group 1: Extubation in the operating theatre; Group 2: Extubation on intensive care unit), patient survival and incidence and indication of reintubation/tracheotomy. Recipient data (age, gender, indication, first and retransplantation) of the surgery (duration of surgery, frequency of transfusion (EK/FFP), cold ischemic time, veno-venous bypass) and the donor organ (donor age, type of donation (postmortal versus living donation) including the type of graft (full size versus split, preservation damage) was analyzed in both groups.

All transplantations were carried out by orthotopic technique. Reperfusion of the graft was simultaneously performed after completion of the portal and arterial anastomo-

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sis. In all patients, the aim of the anesthetic procedure was to immediately extubate all patients in the operating theatre. Thus, extubation was generally performed, if the following criteria were fulfilled: hemodynamic stability, normoxia, normothermia, sufficient tidal volume [VT 5-8 ml/kg], respiratory rate (RR) of less than 20 breaths/min, adequate minute ventilation (VE), and positive gag reflexes. After tracheal extubation, oxygen was given by nasal mask in order to maintain oxygen saturation > 92%. If however extubation was not feasible, further narcotic agents were not administered, thus enabling a primary extubation as early as possible on the transplant intensive care unit.

After extubation on ICU, continuous positive airway pressure (CPAP) (PEEP 7.5 cm H<sub>2</sub>O) was given every 2 hours for 10 minutes. In case of pleural effusion of > 500 ml, a thoracocentesis was performed. Furthermore, routine biopsies were taken and in the event of an infection, an antibiotic therapy was administered [17].

Reasons for reintubation were categorized as follows: surgical, cardiovascular, pulmonary, cerebral, surplus anesthetic and other. In case of long-term artificial ventilation a tracheotomy was performed, usually in dilatation technique [18].

For the statistical analysis a univariate analysis was performed after examining the standard distribution according to the Kolmogorov-Smirnov test (Chi-Quadrat or U-test according to Mann and Whitney for non-standard distribution, or T-test for standard distribution). Thereafter a multivariate logistic regression analysis was conducted, which included all variables that had a probability value  $p \leq 0, 1$  in the univariate analysis. To predict a variable-dependent event with a high sensitivity and specificity, the ROC analysis was conducted. The survival analysis was performed according to the Kaplan-Meier method. Data were expressed as mean  $\pm$  standard deviation. An error probability of  $p < 0, 05$  was considered statistically significant.

## RESULTS

In 76, 8% of the patients, postoperative extubation was performed in the operating theatre (group 1), whereas 194 patients (23, 2%) were extubated on the intensive care ward (group 2). Here long-term artificial ventilation was  $111 \pm 15$  min, however, more than half of the patients (55, 7%) required additional ventilation support for more than 24 h (Table 1).

The reintubation rate was in total 17, 2%, whereas in group 1 reintubation was not required as often as in group 2 (11, 7 versus 35, 6%). Indication of reintubation showed that

pulmonary reasons (particularly atelectasis/secretion) were found statistically significantly more frequently in group 2 (60, 9 versus 41, 3%). The remainder of the causes such as anesthetic surplus, surgical, cerebral or cardiovascular complications were not significantly different between the two groups (Table 2). Altogether 7, 8% of the patients required a tracheotomy for long-term ventilation, whereas patients in group 1 required a tracheotomy statistically more seldom (4, 2 versus 19, 6%).

The 1-, 3- and 5-year survival of patients was 93, 86 and 83% in group 1, whereas patients in group 2 had a 1-, 3- and 5-year survival of 78, 72 and 69%. This difference of  $p=0, 02$  was statistically significant (Fig. 1).

According to the demographic data of the recipients, we had significantly more often patients in group 2 with acute liver failure or retransplantation (initial non-function) requiring LTX, whereas malignant tumors, postnecrotic, or cholestatic cirrhosis were seen more seldom in these patients (Table 3). Whilst the recipient age with  $47, 6 \pm 0, 9$  versus  $50, 6 \pm 0, 4$  years was significantly younger than in group 1, the rate of first transplantations was significantly lower with 70, 1 versus 94, 2%. Only the gender distribution was without statistical differences, although in both groups the male gender prevailed (Table 4A).

We found no differences of surgically associated parameters between the two groups with regard to duration of surgery, cold ischemic time, or utilization of a veno-venous bypass. A highly significant difference was however seen in the amount of intraoperative transfused blood products (Erythrocyte concentration, EK; fresh frozen plasma, FFP). Thus, statistically significantly more EK ( $9, 8 \pm 0, 7$  versus  $4, 3 \pm 0, 2$ ) and FFP ( $15, 7 \pm 1$  versus  $9, 4 \pm 0, 2$ ) were transfused in group 2. A massive transfusion (>15 EK) was also necessary in 20, 1% of the cases, whereas in group 1 it was only necessary in 2, 5% of the cases (Table 4B).

Regarding the donor/graft associated criteria, we found no statistical differences in donor age, type of graft (split or full size), or type of organ donation (postmortal or living donation). Merely the preservation damage, defined as maximal AST in the first 72 h postoperatively, was with  $714 \pm 88$  units/l significantly more pronounced in group 2 than in group 1 with  $453 \pm 36$  units/l (Table 4C).

In the multivariate logistic regression analysis the following parameters showed statistically significant differences between the two groups: Diagnosis of acute liver failure ( $p < 0, 001$ ), retransplantation ( $p < 0, 001$ ), and number of EK's ( $p < 0, 001$ ). Recipient age ( $p = 0, 644$ ), preservation damage ( $p = 0, 603$ ), donor age ( $p = 0, 144$ ) and number of FFP's ( $p = 0,$

**Table 1. Extubation After LTX, Incidence of Reintubation and Tracheotomy**

Parameter	Group 1 Extubation in the OP	Group 2 Extubation on ITS	Total	<i>p</i>
n= (%)	643 (76, 8 %)	194 (23, 2 %)	837	
Duration of postop. ventilation support (h)	0	111, $14 \pm 15, 47$		
Incidence of postop. ventilation support > 24h	0	108/194 (55, 7 %)		
Incidence of reintubation	75 (11, 7 %)	69 (35, 6 %)	144 (17, 2 %)	0, 001
Incidence of tracheotomy	27 (4, 2 %)	38 (19, 6 %)	65 (7, 8 %)	0, 001

Table 2. Indications for Reintubation

Group 1 Extubation in the OP (n=643)		Group 2 Extubation on ITS (n=194)		Total (n=837)	p
<b>Surgical</b>	<b>11 (14, 7%)</b>	<b>Surgical</b>	<b>5 (7, 2%)</b>	<b>16 (11, 1%)</b>	0, 157
Bleeding	10	Bleeding	5		
Vena cava stenosis	1	Vena cava stenosis	0		
<b>Cardiovascular</b>	<b>10 (13, 3%)</b>	<b>Cardiovascular</b>	<b>5 (7, 2%)</b>	<b>15 (10, 4%)</b>	0, 232
Blood pressure decrease	6	Blood pressure decrease	4		
Heart failure	3	Heart failure	0		
Heart attack	0	Heart attack	1		
Pulmonary embolism	1	Pulmonary embolism	0		
<b>Pulmonal</b>	<b>31 (41, 3%)</b>	<b>Pulmonal</b>	<b>42 (60, 9%)</b>	<b>73 (50, 7%)</b>	0, 019
Aspiration	6	Aspiration	5		
Atelectasis / secretion	4	Atelectasis / secretion	13		
Pulmonary edema	4	Pulmonary edema	1		
Pneumonia	9	Pneumonia	8		
Mechanical respiration	8	Mechanical respiration	13		
Bronchospasm	0	Bronchospasm	2		
<b>Cerebral</b>	<b>4 (5, 3%)</b>	<b>Cerebral</b>	<b>5 (7, 2%)</b>	<b>9 (6, 3%)</b>	0, 738
Cerebral bleeding	2	Cerebral bleeding	1		
Postoperative delirium	0	Postoperative delirium	1		
Other	2	Other	3		
<b>Anesthetic</b>	<b>4 (5, 3%)</b>	<b>Anesthetic</b>	<b>1 (1, 4%)</b>	<b>5 (3, 5%)</b>	0, 368
<b>Other</b>	<b>15 (20%)</b>	<b>Other</b>	<b>12 (17, 4%)</b>	<b>27 (18, 8%)</b>	0, 689
<b>Total</b>	<b>75 (11, 7%)</b>	<b>Total</b>	<b>69 (35, 6%)</b>	<b>144 (17, 2 %)</b>	0, 001

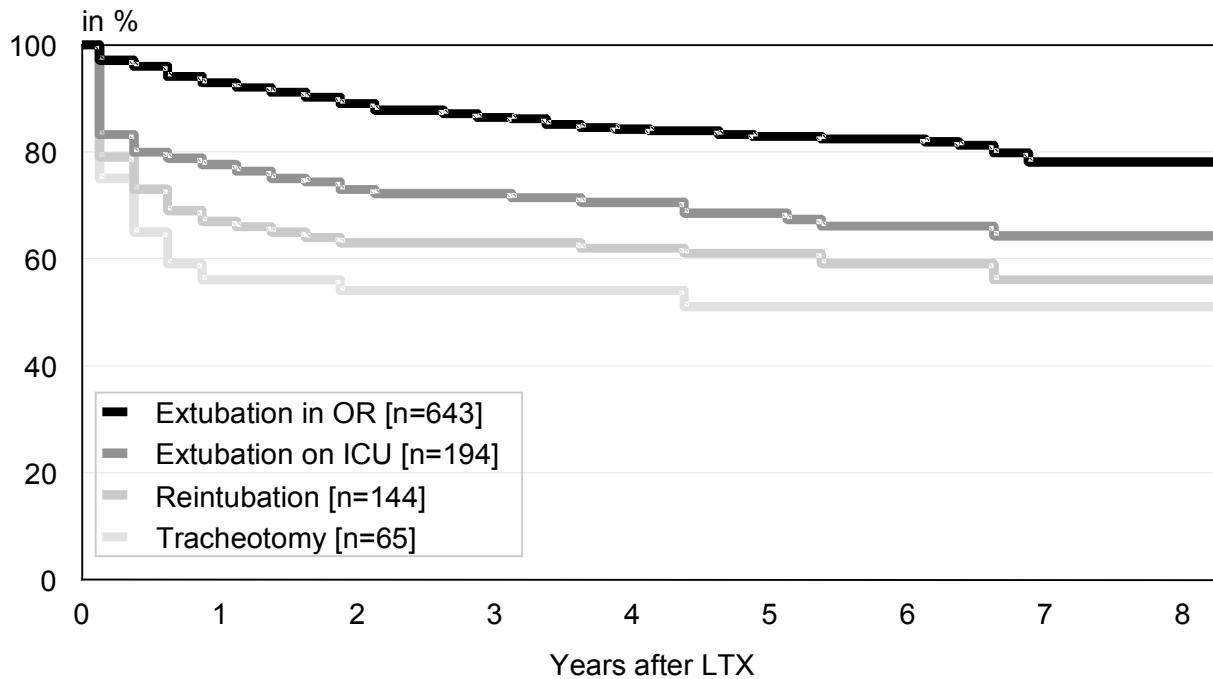
08) did not reach any level of significance. The ROC analysis for the number of transfused EK's indicated for EK's  $\leq 6$  the extubation in the operating theatre OP with the highest sensitivity (78, 9%) and specificity (49, 5%) (under the ROC curve = 0, 703; standard error = 0, 023; 95% confidence interval = 0, 671-0, 734).

## DISCUSSION

The current management in many transplantation centers encourages the early withdrawal of the respirator after successful orthotopic liver transplantation. Contrary to the already historical protocol to postoperatively ventilate patients up to 48 hours [19, 20], nearly all patients are now extubated within a few hours [4-6, 8, 9, 21].

Liver perfusion and particularly the venous drainage from the graft are in spontaneously breathing patients much better than in patients receiving mechanical ventilation [10]. Donor organs damaged due to cooling and transportation can therefore recuperate much faster from the so-called preservation damage, a factor which contributes significantly towards the recovery of the recipient [11, 22]. In this regard, Biancofiore *et al.* reported on significantly lower mortality rates of recipients who were extubated in the operating theatre (1%) compared to recipients with primary extubation within the first 24 hours postoperatively (4%) and those with ventilation times of over 24 hours (42%) [14].

Based on the positive experience of individual transplantation centers, the extubation time point after liver transplantation has been forwarded to take place in the operation thea-



**Fig. (1).** Patient survival after LTX.

ter. This approach was associated to be safe for the recipient, without any increased incidence for reintubation [13, 14, 23], and is applicable for both the pediatric liver transplantation as well as the living-related liver donation [12, 16, 24]. Further advantage is the reduction in the costs due to the decreased utilization of intensive capacities, which are noted in an American study to be approximately 13% of the total costs of a liver transplantation [25].

However, all patients can not get benefited from this fast tracking concept, as can be see in our patient collective, where primary extubation in the operating theatre failed in approximately 20 to 25% of all the patients (Fig. 2) [5, 8, 12, 14-16, 25].

Looking for reasons for this failure lead us to initiate a uni- and multivariate retrospective analysis of our patient collective (n=837). This analysis revealed that the diagnosis for retransplantation and acute hepatic failure, Child C status of the recipient as well as the transfusion of > than 7 EK's have variables which statistically seen are not suitable for primary extubation after orthotopic liver transplantation. Interestingly, preservation damage has no influence on a successful extubation in the operating theatre, as well as the use of a veno-venous bypass. The veno-venous bypass was of particular interest, since the heat exchanger can be connected to the veno-venous bypass, which prevents patients from cooling off during surgery. The warm blankets used nowadays are apparently more than adequate to maintain a constant body temperature up until the end of surgery.

Compared to the literature, our results show that especially patients during a reduced condition, for example during a restricted cerebral function, cannot participate in the fast tracking concept. Here encephalopathy seems to play an important role. This also applies for Child C patients and recipients with acute hepatic failure or retransplantation (mostly due to INF) [26], who in our analysis could only be

extubated on the intensive care unit. Mandell *et al.* reported by means of a multivariate logistical regression analysis of 147 patients, that encephalopathy and body mass index (>35) were criteria for failure of primary extubation in the operating theatre [27]. O'Meara *et al.* reported on similar findings in pediatric transplantations [24], and Biancofiore *et al.* reported of a multivariate logistical regression analysis of 168 patients who received primary extubation within the first three postoperative hours [14].

We can now show from an earlier study that intraoperative administration of more than 15 EK with a ventilation time of over 24 hours after transplantation is statistically significant [17]. With the administration of more than 12 EK, extubation after transplantation was not possible during the first 3 hours [6]. The current ROC analysis showed that only an intraoperative administration with  $\leq 6$  EK allowed for primary extubation in the operating theatre with a high sensitivity and specificity. This underlines the importance of blood saving surgery, which is according to us the only really influencing variable for extubation in the operating theatre, since the diagnosis nor the Child status of the recipient can be influenced by the transplant team.

To conclude, the majority of patients can be extubated after liver transplantation already in the operating theatre, however, this concept does not increase the rate of reintubations (Fig. 2) [14, 17, 25]. This concept should be enforced or rather introduced in all relevant transplant centers, so that fast tracking concepts could receive the approval of all involved disciplines [28]. Presently only 6, 7% (1 of 15!) of all transplant centers uses this concept, which was the outcome of a published survey in which 15 out of 24 German anesthesiological clinics responded [7]. A learning curve as well as the barrier of acceptance is of importance as already mentioned by Biancofiore *et al.* [14] and Perkins [28]. In our own clinic we also observed a comparable connection after

Table 3. Indications for LTX

Group 1 Extubation in the OP (n=643)		Group 2 Extubation on ITS (n=194)		Total (n=837)	<i>p (Uni-Variate)</i>
<b>Postnecrotic cirrhosis</b>	<b>353 (54,9 %)</b>	<b>Postnecrotic cirrhosis</b>	<b>64 (33 %)</b>	<b>417(49,8%)</b>	0,001
HBV	55	HBV	15		
HCV	92	HCV	22		
Alcohol toxic	152	Alcohol toxic	20		
Cryptogene	34	Cryptogene	7		
Autoimmune	20	Autoimmune	0		
<b>Cholestatic necrosis</b>	<b>69 (10,7 %)</b>	<b>Cholestatic necrosis</b>	<b>11 (5,7 %)</b>	<b>80 (9,6%)</b>	0,036
PBC	36	PBC	5		
PSC	33	PSC	6		
<b>Malignant tumors</b>	<b>119 (18,5 %)</b>	<b>Malignant tumors</b>	<b>22 (11,3 %)</b>	<b>141 (16,8%)</b>	0,019
HCC	105	HCC	21		
Bile duct tumors	14	Bile duct tumors	1		
<b>Acute liver failure</b>	<b>8 (1,2 %)</b>	<b>Acute liver failure</b>	<b>30 (15,5 %)</b>	<b>38 (4,5%)</b>	0,001
<b>Retransplantation</b>	<b>37 (5,8 %)</b>	<b>Retransplantation</b>	<b>58 (29,9 %)</b>	<b>95 (11,2%)</b>	0,001
INF	3	INF	28		
Occlusion of A. hepatica	9	Occlusion of A. hepatica	8		
ITBL	8	ITBL	4		
Rejection	8	Rejection	6		
HBV/HCV recurrence	5	HBV/HCV recurrence	7		
Other	4	Other	5		
<b>Various</b>	<b>57 (8,9 %)</b>	<b>Various</b>	<b>10 (5,2 %)</b>	<b>67 (8%)</b>	0,754
Budd-Chiari	10	Budd-Chiari	2		
M. Osler	4	M. Osler	1		
Cystic liver	12	Cystic liver	4		
$\alpha$ 1-Antitrypsinmangel	4	$\alpha$ 1-Antitrypsinmangel	0		
Morbus Wilson	4	Morbus Wilson	2		
Other	23	Other	1		

Table 4. Demographic data – (A) Recipient, (B) Operation, (C) Donor/ Graft

A

Recipient	Group 2 Extubation in the OP	Group 2 Extubation on ITS	Total	<i>p (Uni-Variate)</i>
Sex (male / female)	383 / 260	107 / 87	490 / 347	0, 274
Recipient age (years)	50, 6 ± 0, 4	47, 6 ± 0, 9	49, 9 ± 0, 4	0, 007
First transplantation (n= / %)	606 / 94, 2	136 / 70, 1	742 / 88, 6	0, 001
Retransplantation (n= / %)	37 / 5, 8	58 / 29, 9	95 / 11, 4	

B

Operation	Group 1 Extubation in the OP	Group 2 Extubation on ITS	Total	<i>p (Uni-Variate)</i>
Duration of Surgery (min)	310 ± 3	324 ± 8	313 ± 3	0, 371
Amount of EK (Units)	4, 3 ± 0, 2	9, 8 ± 0, 7	5, 6 ± 0, 2	0, 001
Amount FFP (Units)	9, 4 ± 0, 2	15, 7 ± 1	10, 8 ± 0, 3	0, 001
Massive transfusions (n= / %)	16 / 2, 5	39 / 20, 1	55 / 6, 6	0, 001
Massive infusions (n= / %)	89 / 13, 8	71 / 36, 6	160 / 19, 1	0, 001
Cold ischemic time (min)	516 ± 8	527 ± 15	518 ± 7	0, 634
Veno-venous bypass (n= / %)	521 / 81	159 / 82	680 / 81, 2	0, 536

C

Donor/Graft	Group 1 Extubation in the OP	Group 2 Extubation on ITS	Total	<i>p (Uni-Variate)</i>
Donor age (years)	46 ± 0, 7	43, 52 ± 1, 2	45, 42 ± 0, 6	0, 083
Post-mortal donation (n= / %)	577 / 89, 7	180 / 92, 8	757 / 90, 4	0, 206
Living related conation (n= / %)	66 / 10, 3	14 / 7, 2	80 / 9, 6	
Full size Organ (n= / %)	561 / 87, 3	176 / 90, 7	737 / 88, 1	0, 191
Split Organ (n= / %)	82 / 12, 8	18 / 9, 3	100 / 11, 9	
Split-Organ (n= / %)				0, 765
• post-mortal donation	21 / 3, 3	4 / 2, 1	25 / 3	
• living donation	61 / 9, 5	14 / 7, 2	75 / 9	
Preservation damage (U/l)	453 ± 36	714 ± 88	513 ± 35	0, 003

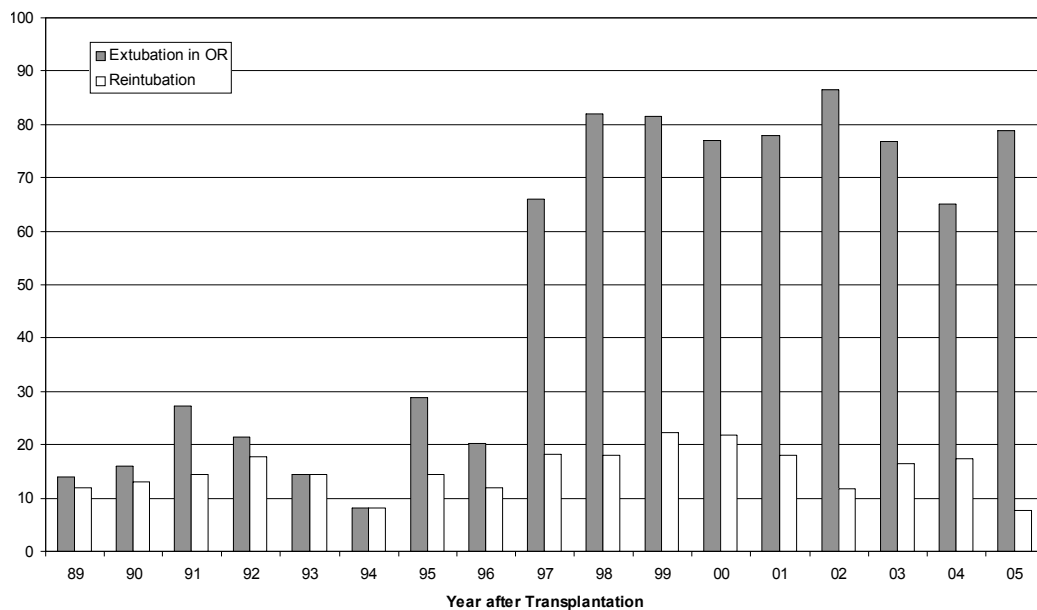


Fig. (2). Rate of extubation in the OR (%) and reintubation (%) during the process.

the first analysis of our patients (OLT 1988-1996) [17], without making substantial changes in the management, where the extubation rate of approximately 20% increased almost to 80% during the following years (Fig. 2).

In summary, the concept of immediate tracheal extubation in liver transplantation is safe and feasible in the vast majority of patients. It may lead to a better patient outcome and at the same time may reduce the overall costs of postoperative care, however, it should not become a tool to stratify between high and low cost recipients. In consequence, immediate tracheal extubation has become the desirable goal for anesthesiologists as well as for transplant surgeons.

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