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Improved hemostasis with major hepatic resection in the current surgical era

Christopher W Mangieri [a,*], Matthew A Strode [a,b], Bradley C Bandera [a]

[a] Department of Surgery, Dwight D. Eisenhower Army Medical Center (DDEAMC), Fort Gordon, GA 30809, USA
[b] Department of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY 14203, USA

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ABSTRACT

Background: Major hepatic resection, predominantly performed for oncologic intent, is a complex procedure with the potential for severe intraoperative hemorrhage. The current surgical era has the ability to improve hemostasis throughout the performance of major hepatic resections which decreases blood transfusions and the detrimental effects associated with transfusion. We evaluated hemostasis and outcomes in the current surgical era of performing hepatic resections.

Methods: Utilizing the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database all major hepatic resections performed between 2012 and 2016 were analyzed in regards to hemostasis. Hemostasis was evaluated by the need for and magnitude of blood transfusions. Additional perioperative variables (including operative time, length of hospital stay, and mortality rates) were analyzed to assess for outcomes with hemostasis. The NSQIP results were compared to previous publications involving major hepatic resections to detect improvement in hemostasis and outcomes in the current surgical era.

Results: A total of 22777 major hepatic resections met the inclusion criteria for analysis in the NSQIP database. An additional 21198 cases were compiled within the selected publications for comparative analysis. The transfusion rate in the current surgical era was 13.3% versus 38.7% in the previous era ($P = 0.0001$). When a transfusion was required in the current surgical era there was a two-fold reduction in the number of units transfused (1.5 U vs. 3.8 U, $P = 0.0001$). Statistically significant improvements in operative time and length of hospital stay were presented within the current surgical era ($P = 0.0001$). When a transfusion was required there was an increased relative risk score of 7 for mortality (4.9% vs. 0.7%, $P = 0.0001$), however, improvement in mortality rates did not reach statistical significance across surgical eras (1.3% vs. 4.0%, $P = 0.0001$).

Conclusions: The conduct of major hepatic resection in the current surgical era is more hemostatic. Correlated with improved hemostasis are better outcomes for both clinical and financial endpoints. These findings should encourage continued and increased performance of major hepatic resections.

Introduction

Hepatic resection continues to evolve as surgeons become more proficient in complex hepatobiliary procedures. Over the past several decades hepatic resections have greatly increased in volume worldwide [1]. Major factors in the ability of surgeons to perform advanced hepatic resections are the improved surgical techniques and instruments available to facilitate those cases [2,3]. It took nearly a century for hepatic surgery to become prevalent following the first large series of hepatic resections reported by Keen in 1899 [4]. Until a better understanding of hepatic anatomy by Couinaud and modifications of the Pringle maneuver to control blood loss, hepatic surgery was nearly non-existent until the end of the 20th century due to disastrous morbidity and mortality rates (mainly secondary to massive hemorrhage) [5–7]. With the development of advanced techniques and equipment to control hemorrhage combined with the ability to safely resect large liver volumes, hepatic surgery started to flourish. Fortner and Blumgart concisely stated that hepatic surgery "had evolved one surgical lifetime" at the start of the 21st century [7].

The current surgical literature routinely cites mortality rates less than 3% with less than 25% complication rate for elective hepatic surgery [8–10]. The increased safety of hepatic resections is directly correlated with the increased number of hepatic

* Corresponding author.
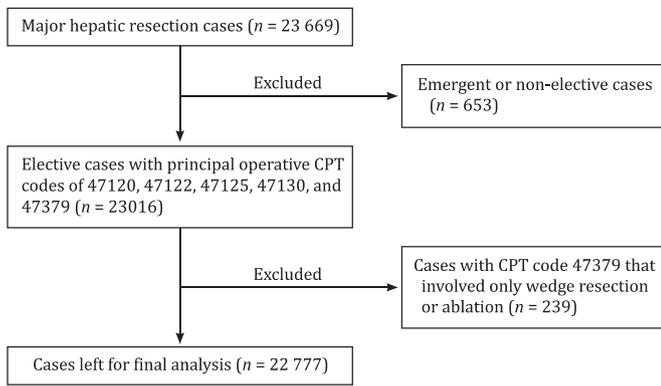*E-mail address:* christopher.w.mangieri.mil@mail.mil (C.W. Mangieri).

Fig. 1. Flow chart of patient selection procedures.

surgeries performed annually [11]. However, the risk and actual occurrence of severe hemorrhage during major hepatic resection continues to plague these operations [12]. Several novel techniques and instruments have been introduced within the past decade, which have significantly decreased intraoperative blood loss with hepatic surgery; most notably anesthesia controlled low central venous pressure (CVP) and saline-coupled dissectors [13–16]. The majority of the published literature evaluating hemostasis with hepatic surgery predates these newer methods of performing more bloodless hepatic surgery. Our hypothesis is with the utilization of advanced surgical techniques and equipment major hepatic surgery is more hemostatic with better clinical outcomes. To our knowledge, this is the largest review of major hepatic resections that has been performed in regard to hemostasis and clinical outcomes with over 40000 cases analyzed.

Methods

This is a retrospective review utilizing the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database. NSQIP is a nationally validated risk-adjusted registry that collects a comprehensive list of patient comorbidities, perioperative variables, and 30-day postoperative outcomes from overall one million annual surgical procedures from approximately 700 participant hospitals in North America [17,18]. NSQIP data has been demonstrated to be of high quality permitting scientific research [19]. Major hepatic resections recorded in NSQIP from 2012–2016 were extracted and analyzed using the principal operative Current Procedural Terminology (CPT) codes 47120, 47122, 47125, 47130, and 47379.

A total of 23669 major hepatic resection cases were contained within the NSQIP registry. Several exclusion criteria were utilized. All emergent or non-elective procedures were excluded. Cases with the principal operative CPT code of 47379, laparoscopic hepatic resection, were further queried to their secondary and tertiary CPT codes. Those cases with secondary or tertiary CPT codes that included minor procedures such as wedge biopsies or ablation procedures were also excluded. During that additional query of the secondary and tertiary CPT codes for laparoscopic procedures the specific type of hepatic resection was sought. Unfortunately, less than 5% of laparoscopic cases had modifying CPT codes that allowed detection of the specific resection. For all of the cases with modifying CPT codes that specific procedure performed laparoscopically was a partial lobectomy. Following exclusion criteria filtration, a total of 22777 major hepatic resection cases were left for final analysis (Fig. 1).

The most relevant preoperative variables recorded in NSQIP regarding effect on operative hemostasis were analyzed. Those variables were PRPLATE (preoperative platelet count) and PRINR (preoperative INR). Determination of hemostasis was provided by the OTHBLEED variable. OTHBLEED records if any blood transfusion (to include whole blood, packed red blood cell, fresh frozen plasma, or cryoprecipitate) and the number of units transfused, was given intraoperative and up to 72 h postoperatively. We focused particularly on transfusion of packed red blood cells (PRBCs). NSQIP does not record the estimated operative blood loss from operative reports. The operative time, length of hospital stay, and 30-day mortality rates included in the NSQIP database were also analyzed. Postoperative diagnosis classified by the correspondent International Classification of Diseases (ICD) code was also evaluated.

For comparative purposes a literature search was performed for major hepatic resections that included hemostasis and transfusion. Any publication considered for comparison had to include at least 500 cases. The literature search returned eight publications meeting the criteria. Those publications used for comparison are listed in Table 1 [10,11,20–25]. Those publications were all retrospective reviews of either national database registries or single tertiary institution records covering the time period from 1986 through 2011. The current surgical era publications were distinguished by studies containing data that correlated with the introduction of techniques and surgical instruments validated for improved hemostasis with major hepatic resection. A total of 21198 major hepatic resection cases were compiled within those publications to compare to the 22777 cases analyzed in this study. The current surgical era publications contained 13726 cases compared to 7472 cases in the previous era publications.

Statistical analysis

Categorical variables were evaluated using Chi-square test. Quantitative variables with one independent variable (with two levels) and one dependent variable were evaluated using Fisher's exact test. Those comparisons that resulted in a significant P value (<0.05) underwent further analysis for strength of association determined by logistic regression modeling and calculating Eta (η) values. Comparisons of quantitative variables were performed with one-way analysis of variance (ANOVA) test. If ANOVA test found a significant difference between variables but with unequal variance as determined by a Levene's test $P < 0.05$ then Games-Howell testing was performed to validate the ANOVA findings. The comparison publication data analysis was performed by formulary test validated in meta-analysis comparisons [26]. All reported P values in this study are two-tailed. All descriptive statistics were processed using the International Business Machines (IBM) Statistical Package for Social Sciences (SPSS) version 25.0 analytical software (IBM Inc., Armonk, NY, USA).

Results

Characteristics for the major hepatic resection cases are presented in Table 2. The diagnoses associated with the cases are presented in Table 3 with the majority of cases involving malignant disease. For NSQIP cases starting in 2014 hepatic parenchyma texture details were recorded with texture subjectively assessed by the surgeon. For those cases 49% had no texture description, 28% were normal, 11% were fatty, 10% were cirrhotic, and 2% were congested. When comparing cases requiring a blood transfusion (PRBCs only) against cases that required no transfusion statistically significant differences were presented. Both operative time (213 ± 112 min vs. 323 ± 149 min, $P = 0.0001$) and length of hospital stay (6 ± 5 d vs. 11 ± 10 d, $P = 0.0001$) nearly doubled in the transfusion arm. The mortality rate increased from 0.7% to 4.9% equating to a relative risk score of 7 when a transfusion was required ($P = 0.0001$).

Table 1

List of publications.

Studies	Title	Publication year
Previous surgical era		
Kooby et al. [21]	Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases	2003
Jarnagin et al. [20]	Improvement in perioperative outcome after hepatic resection: analysis of 1803 consecutive cases over the past decade	2002
Poon et al. [11]	Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database	2004
Virani et al. [10]	Morbidity and mortality after liver resection: results of the patient safety in surgery study	2007
Aloia et al. [25]	Predicting poor outcome following hepatectomy: analysis of 2313 hepatectomies in the NSQIP database	2009
Current surgical era		
Kamiyama et al. [22]	Perioperative management of hepatic resection toward zero mortality and morbidity: analysis of 793 consecutive cases in a single institution	2010
Yamashita et al. [23]	Trends in surgical results of hepatic resection for hepatocellular carcinoma: 1000 consecutive cases over 20 years in a single institution	2014
Ross et al. [24]	Mortality in hepatectomy: Model for End-Stage Liver Disease as a predictor of death using the National Surgical Quality Improvement Program database	2016

Table 2

Characteristics of major hepatic resection in NSQIP database between 2012–2016.

Characteristics	Data ($n = 22777$)		
Cases from 2012	3297		
Cases from 2013	4046		
Cases from 2014	4699		
Cases from 2015	5221		
Cases from 2016	5514		
Overall transfusion rate	18.0%		
Overall mortality rate	1.5%		
Overall operative time (min)	233 ± 127		
Overall length of hospital stay (d)	7 ± 7		
PRBC transfusion (U)	2.0 ± 2.5		
	No transfusion ($n = 18676$)	PRBC transfusion ($n = 4101$)	*P* value
Preoperative platelet count (10^9/L)	231 ± 85	246 ± 109	**0.0001**
Preoperative INR	1.0 ± 0.2	1.1 ± 0.2	**0.0001**
Operative time (min)	213 ± 112	323 ± 149	**0.0001**
Length of hospital stay (d)	6 ± 5	11 ± 10	**0.0001**
Mortality rate	0.7% (140)	4.9% (199)	**0.0001**

Table 3

Diagnoses associated with major hepatic resection.

Diagnosis	Data ($n = 22777$)
Malignant	13595 (59.7%)
Primary hepatic malignancy	4900 (20.6%)
Hepatocellular carcinoma	3293 (14.5%)
Intrahepatic cholangiocarcinoma	1118 (4.9%)
Unspecified	289 (1.3%)
Metastatic malignancy	8895 (39.1%)
Unspecified metastases	5926 (26.0%)
Gallbladder carcinoma	863 (3.8%)
Colorectal metastases	740 (3.2%)
Extrahepatic cholangiocarcinoma	161 (0.7%)
Carcinoids	223 (1.0%)
Neuroendocrine tumors (excluding carcinoid)	426 (1.9%)
Other metastases	556 (2.4%)
Benign	6878 (30.2%)
Unspecified benign neoplasm	1258 (5.5%)
Hemangioma	562 (2.5%)
Cystic disease	239 (1.0%)
Abscess (including pyogenic, echinococcal, amebic, and fungal)	150 (0.7%)
Living liver donor procedure	74 (0.3%)
Other benign process	4595 (20.2%)
No diagnosis specified	2304 (10.1%)

Preoperative factors that could lead to increased risk of bleeding were statistically not homogenous between transfusion and non-transfusion cases. The INR level in transfusion arm was higher than 1.1 [27]. Linear regression modeling and η value calculation assessed the strength of association with INR level and transfusion requirement. No strong correlation was present with the linear regression *R* value (0.2) and with *η* value (0.15).

The specific type of major hepatic resections were compared against each other. The results from the inter-hepatectomy analysis are shown in Tables 4 and 5. More radical surgery elements were recognized about the risk for hemorrhage requiring transfusion than previous findings [28]. As the complexity of hepatic resections increased there was a correlative increase in the transfusion rate, operative time, length of hospital stay, and mortality risk

Table 4
Characteristics of specific hepatic resections in NSQIP database between 2012–2016.

Characteristics	Partial lobectomy (CPT 47120) ($n=13426$)	Total left lobectomy (CPT 47125) ($n=1934$)	Total right lobectomy (CPT 47130) ($n=3657$)	Trisegmentectomy (CPT 47122) ($n=1642$)	Laparoscopic procedure (CPT 47379) ($n=2118$)	P value
PRBC transfusion rate	14.7%	21.5%	29.6%	34.8%	2.8%	**0.0001**
Operative time (min)	217 ± 112	264 ± 129	293 ± 125	330 ± 140	123 ± 86	**0.0001**
Mortality rate	1.0%	1.3%	2.7%	3.9%	1.0%	**0.0001**

Table 5
Specific hepatic resections comparison: transfusion versus no transfusion cases.

Primary surgery	No transfusion	PRBC transfusion	P value
Partial lobectomy (CPT 47120)			
Number of cases	11455	1971	**0.0001**
Preoperative platelet count (10^9/L)	228 ± 83	239 ± 109	**0.0001**
Preoperative INR	1.0 ± 0.2	1.1 ± 0.2	**0.0001**
Operative time (min)	203 ± 100	294 ± 141	**0.0001**
Length of hospital stay (d)	6 ± 5	9 ± 9	**0.0001**
Total left lobectomy (CPT 47125)			
Number of cases	1519	415	**0.0001**
Preoperative platelet count (10^9/L)	237 ± 85	258 ± 112	**0.0001**
Preoperative INR	1.0 ± 0.2	1.1 ± 0.2	**0.0001**
Operative time (min)	246 ± 118	329 ± 145	**0.0001**
Length of hospital stay (d)	7 ± 5	10 ± 13	**0.0001**
Total right lobectomy (CPT 47130)			
Number of cases	2574	1083	**0.0001**
Preoperative platelet count (10^9/L)	232 ± 87	250 ± 109	**0.0001**
Preoperative INR	1.0 ± 0.1	1.1 ± 0.2	**0.0001**
Operative time (min)	274 ± 108	341 ± 149	**0.0001**
Length of hospital stay (d)	8 ± 6	12 ± 11	**0.0001**
Trisegmentectomy (CPT 47122)			
Number of cases	1070	572	**0.0001**
Preoperative platelet count (10^9/L)	239 ± 94	257 ± 108	**0.0001**
Preoperative INR	1.0 ± 0.2	1.1 ± 0.2	**0.0001**
Operative time (min)	298 ± 122	391 ± 151	**0.0001**
Length of hospital stay (d)	9 ± 7	12 ± 10	**0.0001**
Laparoscopic procedure (CPT 47379)			
Number of cases	2058	60	**0.0001**
Preoperative platelet count (10^9/L)	235 ± 87	222 ± 120	**0.0001**
Preoperative INR	1.0 ± 0.2	1.1 ± 0.2	**0.0001**
Operative time (min)	120 ± 82	229 ± 130	**0.0001**
Length of hospital stay (d)	3 ± 3	11 ± 15	**0.0001**

($P=0.0001$). There was a similar trend of outcomes when evaluating the effect of transfusions with specific procedures. When a transfusion was required there was a negative effect on all measured perioperative variables ($P=0.0001$). Analysis of the preoperative variables associated with increased bleeding risk were also almost identical. Again, the average INR for transfused cases was higher than the no transfusion cases with all INR averages below the coagulopathic level (1.5). Logistic regression modeling and calculation of η values for determination of strengths of association with INR and transfusion again were weak in the specific procedure analyses with values less than 0.1 and 0.3, respectively.

The final analytics compared the current to the previous surgical era. A total of 43975 major hepatic resection cases were compared between all the studies. Improved hemostasis was presented in the current surgical era. There was a decreased transfusion rate of 38.7% versus 13.3% between the eras ($P=0.0001$). That improvement in transfusion rates is reflected in Fig. 2A. The number of units transfused also decreased significantly in the current surgical era with a greater than two-fold reduction (1.5 U vs. 3.8 U, $P=0.0001$). There was an improved mortality rate in the current surgical era that did not reach statistical significance (1.3% vs. 4.0%, $P=0.318$). The overlap of mortality rate confidence intervals is depicted in Fig. 2B. Differences in operative and recovery time reached statistical significance, with improvements of averaged approximately 20 min ($P=0.039$) and 2 hospital days ($P=0.0001$), respectively.

Discussion

The Achilles heel of hepatic resection is severe hemorrhage due to the volume of blood the liver receives and the difficultly in controlling the hepatic vasculature [7,12,29,30]. Hepatic surgeons have constantly been trying to improve hemostasis since the onset of liver surgery. Once clamping techniques, such as the Pringle maneuver, became more prevalent, intraoperative blood loss as well as the associated severely high mortality rates significantly decreased thus making hepatic surgery more acceptable [8,30–32]. Additional techniques and advanced surgical instruments in the current surgical era make hepatic resection even safer regarding blood loss. Yet, major hepatic resections continue to have an increased bleeding risk compared to other major intra-abdominal procedures [33,34]. Even more salient is the finding that any blood transfusion with hepatic resections correlates with increased mortality rates, major complications, and recurrence of malignant disease [20,21,35–37].

Our evaluation of major hepatic resections in the current surgical era reveals a clear improvement in hemostasis with a nearly three-fold decrease in the blood transfusion rate. That decreased need for transfusions should result in improved outcomes. NSQIP evaluation limits outcome analysis to simple operative characteristics and 30-day postoperative variables. While a statistically significant improvement in operative time and length of hospital stay was presented in the current surgical era improvement in the
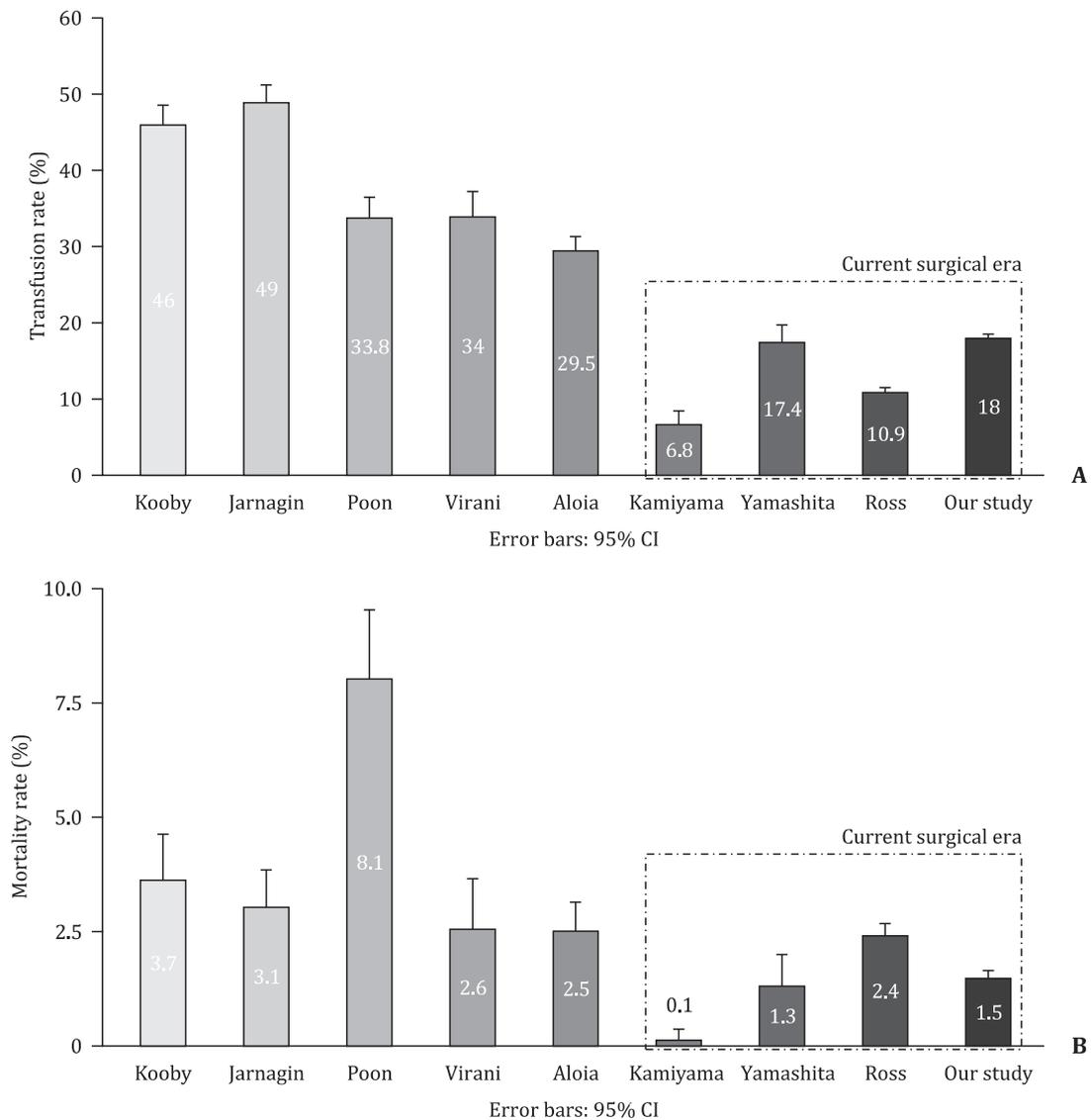
Fig. 2. Transfusion (**A**) and mortality (**B**) rates of previous versus current surgical era.

mortality rates did not reach statistical significance. Certainly, the decrease in mortality rates is not solely due to improved hemostasis but multi-factorial with concurrent improvements in surgical approach and anesthesia care. Further research is warranted to assess if improved hemostasis in the current surgical era still parallels with variables previously studied such as major complications and malignancy recurrence.

The re-evaluation of recurrence of malignancy is particularly prudent since the largest percentage of major hepatic resections are performed for oncologic intent based on NSQIP figures (approximately 60%). As previously stated the association of blood transfusions and increased recurrence of malignancy with decreased survival following hepatic resection would be interesting to revisit [21,35,36]. Adding more intrigue for further scientific inquiry is that published reports of improved survival for both primary and secondary malignancies of the liver treated with primary hepatic resection correspond with the same timeframe of improved hemostasis with hepatic surgery [38,39]. Our study found that laparoscopic major hepatic resection had the lowest transfusion rate at 2.8%. A couple studies have demonstrated improved disease-free survival for laparoscopic hepatic resection performed with oncologic intent [40,41]. A possible component to that improved

disease-free survival could be the improved hemostasis. Further research is required to delineate the validity of those possibilities.

The most commonly cited factors for improved hemostasis in the current surgical era with hepatic surgery is the utilization of anesthesia controlled low CVP and advanced surgical instruments [13–16,42–44]. Controlling intraoperative CVP between 3–5 mmHg results in less bleeding compared to CVP greater than 5 mmHg when a hepatic vessel is injured [43]. Several randomized control trials have confirmed the efficacy of improved hemostasis with anesthesia controlled low CVP [13,14]. The controlled CVP technique in our opinion is the strongest factor for improved hemostasis owing to the simple fact if there is less blood in the hepatic vessels and parenchyma that inherently decreases blood loss with the use of reasonable dissection techniques. There is a gambit of various surgical dissectors touted as improving hemostasis during hepatic resection. The majority of publications stating the efficacy of these instruments are small retrospective single-institution studies. That renders it difficult to make definitive statements about advanced surgical instruments improving hemostasis [45]. The class of instruments with the largest support in the literature are the saline-coupled dissectors [15,16,45–48]. Our own anecdotal experience agrees with saline-coupled dissectors

as the most hemostatic in the current armamentarium. Two of the selected studies for our comparative analysis, Kamiyama et al. [22] and Yamashita et al. [23], contained cases bridging the previous and current surgical eras for hepatic surgery. In both of those studies the authors cited the introduction of anesthesia controlled techniques combined with new advanced surgical instruments as factors for improved hemostasis and outcomes [22,23]. Yamashita et al. [23] went into further detail grouping his cases to more objectively demonstrate how incorporating advanced techniques and tools improved outcomes.

The assumption of this study is surgeons performing major hepatic resection in the current era are already incorporating the previously described evidence-based practices. Since the NSQIP database is a national registry, precise details of operations, utilization of controlled CVP and surgical instruments used, are unable to be included in the collection variables. Thus, it is impossible to unequivocally confirm our assumption with the informational restrictions of the NSQIP registry. A disadvantage of using sources like NSQIP is that the quality of the data analyzed is potentially sacrificed for the "*n*" provided.

Our analysis cannot definitely prove that incorporation of evidence-based practices is the causality for improved hemostasis and outcomes in the current surgical era. What is very strong in our findings is for whatever the factors may be the surgical community is improving in our performance of major hepatic resections. Hemostasis is undeniably better controlled in the current era. About 82% of patients did not require a transfusion in the cases we analyzed. The current era more than halved the transfusion rate and blood unit utilization of the previous era. Even the most complex hepatic resection, trisegmentectomy, performed in the current era has a transfusion rate which is below the average rate for any hepatic resection performed in the previous era. Blood transfusions are not risk free with infectious and immunological complications in addition to the growing shortage of transfusion resources [49,50]. Certainly negating transfusion use benefits patients [51].

Seemingly modest improvements in operative time and length of hospital stay of 20 minutes and 2 hospital days respectively translate into potentially significant financial benefits. The estimated cost of one minute in the operating room in the United States equates to $122 making a 20-minute change a $2440 difference in operative costs [52]. Based on Kaiser State Health Facts the average daily cost of an inpatient admission is $2085.66 [53]. The combined financial differentiation is $6611.32. When multiplied by the annual number of major hepatic resections performed the final healthcare costs savings is approximately $36.5 million. With the en vogue discussion of healthcare cost containment that is not an insignificant number. Decreased medical costs also benefit the individual patient [54].

In conclusion, "*Primum non nocere*" is the most popularized line from the Hippocratic oath. It took nearly a century for hepatic surgery to meet that standard of first do no harm. It is unrealistic to expect that operating on the liver will ever be completely bloodless. Major hepatic resection will always remain a complex procedure with intrinsic hemorrhagic risks. However, the current surgical era with multiple adjuncts to provide hemostasis presents discernable evidence that hepatic resection can continue to become safer, more efficient, and produce better outcomes.

Contributors

MCW proposed the study, gathered the data, and performed the initial data analysis. All the authors contributed to the design and interpretation of the study and to further drafts. MCW is the guarantor.

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