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The safety, efficacy and cost-effectiveness of intraoperative cell-salvage in metastatic spine tumour surgery

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42 **ABSTRACT**

43 **Background context:** Metastatic spine tumour surgery (MSTS) is associated with substantial blood

44 loss therefore leading to high morbidity and mortality. While intraoperative cell salvage with

45 leucocyte depletion filter (IOCS-LDF) has been studied as an effective mean of reducing blood loss

46 in other surgical settings, including the spine, no study has yet analysed the efficacy of re-infusion of

1

1 salvaged blood in reducing the need for allogenic blood transfusion in patients who have had surgery

2 for MSTS.

3 **Purpose:** To analyse the efficacy, safety and cost effectiveness of using IOCS-LDF in MSTS.

4 **Study design/ Setting:** Retrospective controlled study

5 **Patient sample:** 176 patients undergoing MSTS

6 **Methods:** All patients undergoing MSTS at a single centre between February 2010 and December

7 2014 were included in the study. The primary outcome measure was the use of autologous blood

8 transfusion. Secondary outcome measures included hospital stay, survival time, complications and

9 procedural costs. The key predictor variable was whether or not IOCS-LDF was utilised during

10 surgery. Logistic and linear regression analyses were conducted by controlling variables such as

11 tumour type, number of diseased vertebrae, approach, number and site of stabilised segments,

12 operation time, pre-operative anaemia, ASA grade, age, gender and BMI. No funding was obtained

13 and there are no conflicts of interest to be declared.

14 **Results:** Data included 63 cases (IOCS-LDF) and 113 controls (non IOCS-LDF). IOCS-LDF

15 utilisation was substantively and significantly associated with a lower likelihood of allogenic blood

16 transfusion (OR=0.407, p=0.03). IOCS-LDF was cost neutral (p=0.88).   Average hospital stay was

17 3.76 days shorter amongst IOCS-LDF patients (p=0.03). Patient survival and complication rates were

18 comparable in both groups.

19 **Conclusions:** We have demonstrated that the use of IOCS-LDF in MSTS reduces the need for post-

20 operative allogenic blood transfusion whilst maintaining satisfactory post-operative haemoglobin.

21 We recommend routine use of IOCS-LDF in MSTS for its safety, efficacy and potential cost benefit.

22

23 **Keywords:** "intraoperative cell salvage", "intraoperative blood salvage autotransfusion", "autologous

24 transfusion", "autotransfusion", "malignant tumour", "tumour surgery", "cell saver", "blood loss in

25 spinal metastatic surgeries, and "leucocyte depletion filter"

2

1 **INTRODUCTION**

2

3 Metastatic spine tumour surgery (MSTS) aims to decompress neural structures, preserve cord

4 function, stabilise the spine and confirm diagnosis prior to further oncological treatment. Whilst

5 recent advances in perioperative care, spinal instrumentation and surgical techniques have led to

6 improved clinical outcomes in MSTS, the peri-operative and postoperative risks remain high.[1, 2]

7 Surgical treatment of MSTS is often associated with substantial blood loss and need for autologous

8 blood transfusion, both of which contribute to high morbidity and potential mortality associated with

9 these surgeries. In a meta-analysis published in 2013,Chen et al[3] found a mean blood loss of 2180ml

10 in spinal tumour surgeries with a possibility of catastrophic blood loss of more than 5000ml in 12% of

11 patients.[3]

12 A number of peri- and intra-operative strategies exist to reduce the risk of blood loss. Their aim is to

13 minimize the need for allogeneic blood product transfusion, decrease total blood loss, and reduce cost.

14 [4] Additionally, they maintain high/adequate post-operative haemoglobin which potentially benefits

15 patient recovery and could affect postoperative complication rates.[5]

16 Intraoperative cell salvage (IOCS) involves the collection of shed surgical blood, filtration, and

17 reinfusion to the patient and reduces the need of allogeneic blood transfusion.[6] It has been

18 demonstrated to be a viable option for reduction or avoidance of allogeneic blood product during

19 many oncologic surgeries and may be a lifesaving option for patients who refuse allogeneic blood

20 products.[7]

21 The use of IOCS has been investigated in other oncological surgeries. In gynaecology, hepatic,

22 urological and cardiothoracic setting it has been demonstrated as being safe and efficacious in

23 reducing allogeneic blood transfusion.[6-8]

24 Although IOCS provides benefits, it carries some risks. In paediatric patients transient haematuria,

25 concern for reinfusion of heparinized blood leading to altered haemostasis and alteration in electrolyte

26 balance have been reported.   Furthermore, IOCS is potentially costly, and requires additional

27 personnel intraoperatively.[7]

3

1   In oncological surgeries, efficacy of using the leucocyte depletion filter (LDF) to remove malignant

2   cells from intra-operative cell salvage blood has been studied in vitro and in vivo and reported as a

3   potentially safe.[9] Previous studies have also evaluated the effectiveness of using IOCS with LDF to

4   eliminate tumour cells from salvaged blood in spinal tumour surgeries[10, 11]. However no large

5   scale comparative studies have been published to evaluate the efficacy in reducing the need for

6   autologous blood transfusion or cost effectiveness in spinal tumour surgery.[12]

7   In a systematic review published in 2014, Kumar et al suggested that the evidence base [10, 11] in

8   other oncological surgeries would support the use of IOCS in MSTS but recognised the lack of

9   evidence in this particular patient group.[12]

10   The aim of this study was to evaluate the safety, efficacy and cost effectiveness of IOCS in MSTS.

11

12   **METHODS**

13

14   Data was retrospectively obtained from studying all patients undergoing MSTS at a single tertiary

15   referral centre between February 2010 and December 2014. Case notes and electronic inpatient

16   hospital records were reviewed. All disease related, patient related, surgery related and post-operative

17   charts were reviewed to complete the data.

18   Logistic and linear regression analyses were conducted, considering whether or not an allogenic blood

19   transfusion was given and post-operative haemoglobin levels as primary outcome measures.

20   Secondary outcome measures included length of stay, post-operative survival time, complications and

21   procedural costs. The key predictor variable was whether or not IOCS-LDF was utilised during the

22   surgical procedure.

23   A number of procedural-related, health-related and demographic variables were also initially

24   considered as controlling variables for the primary analyses. Procedural-related variables were: type

25   of tumour (categorised as thyroid/renal or non-thyroid/renal); number of vertebrae (affected spinal

26   levels in the operative field); anatomical region (cervical, cervicothoracic, thoracic, thoracolumbar or

27   lumbar); approach (posterior, anterior or combined); number of stabilised spinal levels and operation

28   time. Health-related variables were: pre-operative anaemia and ASA (American Society of

4

1   Anaesthesiologists) grade.[13] Demographic variables were: age; gender and body mass index

2   (BMI).

3   Data was summarised descriptively. Exploratory procedures were undertaken to assess data

4   distributions, extent of missing data and possible collinearity.

5   Logistic regression analyses were conducted using the allogenic blood transfusion outcome measure.

6   A sequential modelling strategy was utilised with the key predictor variable of IOCS-LDF utilisation

7   included at the highest level of the model hierarchy. All procedural-related variables were then fitted

8   at the second stage of the hierarchy. Health-related variables, ASA grade and anaemia status were

9   fitted at the third level of the hierarchy. Demographic variables of age, gender and BMI were fitted at

10   the fourth (lowest) level of the hierarchy. For hierarchical levels 2-4, stepwise routines were utilised

11   to derive an optimum selection of variables within the level. Final model adequacy was assessed

12   using Nagelkerke's pseudo-R^2 statistic, and the percentage of cases correctly classified by the model

13   was evaluated.

14   Linear regression analyses were conducted on the data using the post-operative haemoglobin level

15   outcome measure utilising the same sequential modelling strategy as for the sequential logistic

16   regression modelling. Cross-validation and diagnostic procedures were conducted on both of the final

17   logistic and linear regression models.

18   Secondary outcomes were assessed using descriptive and univariable methods. Association between

19   IOCS-LDF group and patient survival was assessed using the χ^2 test for association. Associations

20   between IOCS-LDF group, length of hospital stay and total procedural costs were assessed using

21   independent samples t-test.

22   Cost calculation was performed analysing the combined cost of use of IOCS-LDF equipment and cost

23   of allogenic blood.

24

25

26   **RESULTS**

27

5

1   Analysis was conducted on 176 patients, from an original dataset of 178 patients. Two patients were

2   not assigned to an IOCS-LDF group and were excluded from the analysis. Less than 0.5% of the

3   remaining data in total was missing, and imputation methods were not used.

4   Data comprised 63 cases (use of IOCS-LDF) (35.8% of valid cases) and 113 controls (no use of IOCS-

5   LDF) (64.2% of valid cases). Dataset included 106 males (60.2%) and 70 females (39.8%); with a

6   mean age of 63.2 years (SD 12.6 years) (Table 1).

7   Exploratory analyses indicated evidence for collinearity effects between certain variables

8   necessitating the removal of variables corresponding to number of affected vertebrae and anatomical

9   region from subsequent analyses.

10

11   *Analysis of need for allogenic blood transfusion outcome*

12   Using the stepwise modelling strategy within each level of a sequential logistic regression procedure,

13   the Level-2 variable corresponding to approach and stabilised levels entered the model at the 2nd step,

14   following the forced entry of the key predictor variable of IOCS-LDF at step 1. No other variables

15   were included in the model at this step. Both Level-3 variables (ASA grade and preoperative anaemia)

16   were included in the model at the 3rd step. None of the Level-4 variables (demographic variables)

17   were included in the model at the 4th step. Hence, the final model included the variables IOCS-LDF,

18   approach, number of stabilised levels, ASA grade and preoperative anaemia (Table 2).

19   IOCS-LDF was found to be substantively and significantly associated with this outcome, as were

20   number of stabilised levels, anaemia status and ASA grade. Approach was substantively associated

21   with the need for allogenic blood transfusion but did not achieve statistical significance at the 5%

22   level.

23   Controlling for other variables, the odds of a patient receiving an allogenic blood transfusion were

24   59% higher in cases where IOCS-LDF was not utilised than when it was utilised. A higher probability

25   of allogenic blood transfusion was found in patients whose procedures involved anterior, rather than

26   posterior approach (not statistically significant), greater extents of spinal fixation, higher ASA grades

27   (indicating worse morbidity) and preoperative anaemia.

6

1   Nagelkerke's pseudo-R^2 statistic for the parsimonious model was 0.276, indicating that the model is a

2   good fit to the data. The model correctly classified 73.4% of cases in the sample. A model derived

3   from a training set comprising 80% of cases correctly classified 70.0% of cases in a validation set

4   comprising the remaining 20% of the sample; indicating good predictive capability. Studentised

5   residuals and Cook's distances were within expectations for all cases, indicating that no data point

6   exerts excessive influence on the model.

7

8   *Analysis of post-operative haemoglobin outcome*

9   Using the stepwise modelling strategy within each level of a sequential regression procedure, the

10   Level-2 variable corresponding to stabilised levels entered the model at the second step, following the

11   forced entry of the key predictor variable of IOCS-LDF at step 1. The Level-3 variable corresponding

12   to anaemia entered the model at the 3rd step. The Level-4 demographic variable gender was included

13   in the model at the 4th step. Hence the final model included the variables IOCS-LDF, stabilised levels,

14   anaemia and gender (Table 3).

15   While the controlling variables corresponding to number of stabilised levels, anaemia and gender

16   were found to be significantly associated with the outcome, the IOCS-LDF variable did not achieve

17   statistical significance at the 5% level, or appear to show any substantive importance. Higher post-

18   operative haemoglobin levels were found in patients whose procedures involved lesser extents of

19   spinal fixation, in those without anaemia and in males. Controlling for other variables, an increase of

20   one stabilised level was associated with a decreased post-operative haemoglobin count of 1.55 units;

21   pre-operatively anaemic patients had 6.9 units post-operative haemoglobin count less than non-

22   anaemic patients; and male patients had 8.7 units post-operative haemoglobin count greater than

23   female.

24   The adjusted (Wherry) R^2 value for the final model was 0.111. Stein's adjusted R^2 statistic for the

25   final model was 0.0863; indicating an adequately performing model with good cross validity

26   predictive power.   Studentised residuals and Cook's distances were within expectations for all cases,

27   indicating that no data point exerts excessive influence on the model. No evidence for violation of

7

1   regression assumptions was detected during residual analysis procedures: residuals were found to be

2   normally distributed and homogeneity of variance was achieved.

3

4   *Analyses of secondary outcomes*

5   The association between patient survival and IOCS-LDF was not significant using a χ^2 test for

6   association ($\chi^2_{(1)}=0.245$; $p=0.620$). Length of stay was 3.76 days shorter on average amongst those

7   for whom IOCS-LDF was utilised (15.9 days) than amongst those for whom IOCS-LDF was not

8   utilised (19.1 days). This difference was statistically significant using an independent samples t-test

9   ($p=0.028$). A 95% confidence interval for the difference was given by (0.34, 6.01).

10   IOCS-LDF costs £128.41 per case. The cost of the allogenic blood is £135.7 for a red blood cell unit,

11   £215.03 for a platelets unit and £29.11 for a unit of fresh frozen plasma. The total procedural cost for

12   patients for whom cell salvage was utilised and for whom IOCS-LDF was not utilised was not

13   significantly different using an independent samples t-test ($p=0.875$).

14   No difference in the peri and post-operative complications was found between the two groups.

15

16

17   **DISCUSSION**

18

19   Blood loss in MSTS is a major complication due to the tumour nature or altered spinal vascular

20   anatomy (dilated epidural veins, hypervascularity and neovascularisation). Controlling blood loss is

21   difficult. To date, very little evidence exists to support the use of IOCS-LDF in MSTS. [14-16]

22   Blood loss can affect patient recovery, delay wound healing and increase the risk of wound infection,

23   ultimately delaying further oncological (radio or chemotherapy) treatment, increasing hospital stay

24   and adding to healthcare costs.[17]

25   The evaluation of the efficacy of blood conservation techniques in MSTS is compounded by many

26   factors that can influence blood loss. These include type of primary tumour (non vascular/vascular),

27   number of affected segments, number of operated levels, operative time and approach. Additionally,

28   health related factors such as pre-operative anaemic status of the patients, ASA grading and BMI are

8

1   also variables that can potentially influence blood loss. This is, to our knowledge, the first study to

2   comprehensively consider and control for these confounding factors in evaluating the use of IOCS-

3   LDF in MSTS.

4   All of these factors have been previously demonstrated as potentially affecting blood loss; Zhenget

5   al[18] reported the factors affecting blood loss and blood transfusion in patients having segmental

6   spinal surgeries as number of levels fused, age, and low preoperative haemoglobin. Many studies

7   have validated to role of BMI and ASA grade as factors which affect intraoperative blood loss.

8   Therefore, in analysing the benefits of intraoperative cell salvage we have controlled for these

9   potentially confounding factors in order to accurately establish the efficacy of IOCS-LDF in reducing

10   the need for allogenic blood transfusion[19-23].

11   The choice of surgical approach is dependent upon the source of compression (anterior or posterior),

12   patient comorbidity, associated deformity, surgeon's experience and spinal instability. Cases with 3-

13   column spinal disease, compression, deformity (kyphosis) and instability can require combined,

14   anterior and posterior, decompression and stabilisation. These procedures are associated with

15   significantly greater morbidity and blood loss, therefore have been controlled for in the analyses.[24-

16   26]

17   To our knowledge, to date, no studies have analysed the cost-effectiveness of IOCS-LDF in MSTS.

18   However, in liver transplant and hepatocellular carcinoma it has been found to be cost-effective.[27,

19   28]. Ubeeetal [29] concluded that the cost benefits of IOCS make this technique economically

20   efficient, clinically effective and an attractive alternative to other methods of transfusion for open

21   radical prostatectomy surgery.[29] Our results show that using IOCS-LDF is potentially cost neutral.

22   The total procedural cost for patients for whom IOCS-LDF was utilised and for whom IOCS-LDF

23   was not utilised was found to be not significantly different. However our study did not include the

24   additional staff cost that can be assicated with use of IOCS-LDF.

25   The short hospital stay is an important focus of modern hospital management with associated

26   reduction in cost and improvements the quality of health care. Our results show that using IOCS is

27   consistent with a reduced hospital stay. Whilst this difference was observed and significant, it is

28   likely that unmeasured factors, rather than the utilisation of IOCS-LDF, have contributed to this

9

1 finding (for example, patients' neurological status). In our study no association was found between

2 patient survival and IOCS-LDF.

3 Whilst our data was analysed retrospectively, missing data was minimal and with the substantial

4 number of patients and an analysis that controls for the majority of the known and measurable

5 confounding factors that can influence blood loss in this type of surgery, our findings would suggest

6 that the routine use of IOCS-LDF in MSTS has clear benefits for both patients and healthcare

7 providers.

8 The National Institute for Health and Care Excellence (NICE) published guidelines endorsing the use

9 of IOCS-LDF for radical prostatectomy and cystectomy.[30] We would advise, based on our

10 findings, the routine use of IOCS-LDF in MSTS.

11

12 **CONCLUSION**

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14 In summary we have demonstrated that the use of IOCS-LDF in MSTS reduces the need for post-

15 operative allogenic blood transfusion whilst maintaining satisfactory post-operative haemoglobin. The

16 use of IOCS-LDF may be cost-effective depending on the personnel set-up. We would recommend

17 routine use of IOCS-LDF in MSTS for its safety and efficacy.

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1   **DECLARATION OF INTERESTS**

2

3   The authors declare they have no conflicts of interest related to this work.

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8   outside the scope of the submitted work.

11

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1   **Table 1: descriptive summary of cohort**

Variable	Cases (n=63)	Controls (n=113)	All patients (n=176)
Gender			
Males (frequency (valid %))	45 (71.4%)	61 (54.0%)	106 (60.2%)
Females (frequency (valid %))	18 (28.6%)	52 (46.0%)	70 (39.8%)
Age (mean (SD))	63.6 (13.8)	64.1 (11.5)	63.6 (12.6)
BMI (mean (SD))	25.9 (4.55)	25.7 (4.58)	25.8 (4.54)
Number of affected vertebrae (median (range))	1 (1-7)	1 (1-4)	1 (1-7)
Number of stabilised levels (median (range))	4 (2-12)	4 (0-11)	4 (0-12)
Operation time (hours) (mean (SD))	4.64 (1.66)	4.04 (1.54)	4.26 (1.62)
ASA score (median (range))	3 (1-5)	3 (1-5)	3 (1-5)
Length of stay in days (mean (SD))	15.9 (7.38)	19.1 (9.96)	17.9 (9.19)
Type of tumour			
Non-thyroid/renal (frequency (valid %))	53 (86.9%)	105 (93.8%)	158 (91.3%)
Thyroid/renal (frequency (valid %))	8 (13.1%)	7 (6.2%)	15 (8.7%)
Approach			
Posterior only (frequency (valid %))	51 (81.0%)	96 (85.0%)	147 (83.5%)
Anterior/both (frequency (valid %))	12 (19.0%)	17 (15.0%)	29 (16.5%)
Level code			
Cervical (frequency (valid %))	3 (4.8%)	11 (9.7%)	14 (8.0%)
Cervicothoracic (frequency (valid %))	7 (11.1%)	9 (8.0%)	16 (9.1%)
Thoracic (frequency (valid %))	28 (44.4%)	52 (46.0%)	80 (45.5%)
Thoracolumbar (frequency (valid %))	16 (25.4%)	35 (31.0%)	51 (29.0%)
Lumbar (frequency (valid %))	9 (14.3%)	5 (5.3%)	15 (8.5%)
Preoperative anaemia			
No anaemia (frequency (valid %))	29 (46.0%)	58 (51.3%)	87 (49.4%)
Anaemia (frequency (valid %))	34 (53.0%)	55 (48.7%)	89 (50.6%)
Surgical complications			
No complications (frequency (valid %))	59 (95.2%)	107 (99.1%)	166 (97.6%)
Complications (frequency (valid %))	3 (4.8%)	1 (0.9%)	4 (2.4%)
Patient survival			
Death recorded (frequency (valid %))	26 (41.3%)	51 (45.1%)	77 (43.8%)
No death recorded (frequency (valid %))	37 (58.7%)	62 (54.9%)	99 (56.2%)
Procedural cost (mean (SD))	GBP351.78 (GBP207.21)	GBP338.42 (GBP314.85)	GBP340.77 (GBP286.67)

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1   **Table 2: Parameter coefficients, confidence intervals and p-values of all variables included in final model**

2   **(blood transfusion outcome measure)**

Variable	Parameter estimate	Odds ratio (OR)	95% confidence interval for OR	P-value
IOCS-LDF	-0.898	0.407	(0.180, 0.920)	0.031
Approach[1]	0.923	2.516	(0.866, 7.304)	0.090
Number of stabilised levels	0.408	1.503	(1.221, 1.852)	<0.001
Anaemia status[2]	1.042	2.836	(1.337, 6.016)	0.007
ASA grade	0.806	2.239	(1.244, 4.031)	0.007

3   [1]Reference category=posterior approach

4   [2]Reference category=no anaemia

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8   **Table 3: Parameter coefficients, confidence intervals and p-values of all variables included in final model**

9   **(post-operative haemoglobin outcome measure)**

Variable	Unstandardised coefficient	95% confidence interval	P-value
IOCS-LDF	-1.568	(-6.708, 3.572)	0.548
stabilised levels	-1.553	(-2.778, -0.328)	0.013
Anaemia[1]	-6.892	(-11.81, -1.97)	0.006
Gender[2]	-8.692	(-13.77, -3.61)	0.001

10   [1]Reference category=no anaemia

11   [2]Reference category=male

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