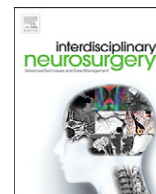


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Cell saver filtering of extravasated rhBMP-2 after degenerative scoliosis reconstruction ☆☆☆★



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ABSTRACT

RhBMP-2 is a bone fusion enhancer commonly used in scoliosis reconstruction surgery. It is delivered via an absorbable collagen sponge but has been known to migrate away from its delivery site. RhBMP-2 extravasation in surgical drainage has been noted during first two days post-surgery. Cell savers are widely used in scoliosis reconstruction to limit transfusion requirements and are commonly deployed in cases where rhBMP-2 is used for fusion augmentation. It is not known whether rhBMP-2 is present in salvaged blood or filtered away during cell saver recycling. Through this case series of four patients who underwent scoliosis reconstruction, we assess cell saver efficacy in filtering rhBMP-2 molecules by quantifying the amount of rhBMP-2 present in salvaged blood obtained after postoperative drainage recycling by OrthoPAT® cell saver and comparing it to rhBMP-2 leakage in postoperative drainage without cell saver recycling. We report an almost 10-fold reduction of rhBMP-2 concentration in salvaged blood obtained after cell saver recycling of postoperative drainage, suggesting cell saver effectiveness in filtering rhBMP-2 molecules.

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Introduction

Recombinant bone morphogenetic protein-2 (rhBMP-2) is a potent bone inducer that has been extensively used in spinal surgery to augment fusion and prevent pseudoarthrosis. FDA approval remains limited to single level anterior lumbar body fusion surgery, however successful results have extended rhBMP-2's off-label usage to numerous spine surgery procedures including multilevel degenerative scoliosis reconstruction with excellent results [1]. To improve osteoinductive potency, rhBMP-2 is delivered intraoperatively via an absorbable collagen sponge (ACS), which increases retention at the fusion site [2]. There are however concerns of rhBMP-2 leakage from the sponge. Results of previous in-vitro and animal studies indicate that a large percentage of implanted rhBMP-2 is released from the

sponge during the first 48 h after surgery [3,4]. It is also during the first two postoperative days (POD) that rhBMP-2 extravasation in surgical drainage was noted after posterolateral fusion surgery [5].

Cell salvage techniques are commonly employed in spinal surgery to salvage patient's red blood cells (RBCs) and reduce transfusion requirements. Blood is salvaged from operative field or less commonly from postoperative drainage. Considering evidence of rhBMP-2 extravasation in surgical drainage and likely leakage into operative field, autologous transfusion using intra or postoperative cell salvage may inadvertently introduce rhBMP-2 molecules into systemic circulation. It is therefore clinically relevant to know whether cell saver devices act as effective filters of rhBMP-2, reducing its concentration in salvaged blood destined for systemic circulation.

In this series we discuss four cases that underwent rhBMP-2 augmented degenerative scoliosis reconstruction. RhBMP-2 recovery was prospectively measured in postoperative drainage and in salvaged blood after drain contents underwent cell saver processing. Our aim was to investigate cell saver efficacy in filtering rhBMP-2 molecules by quantifying the amount of rhBMP-2 present in salvaged blood derived after postop drainage recycling by cell saver and comparing it to rhBMP-2 leakage in drainage without cell saver recycling.

Methods

Four patients (A, B, C and D) that underwent degenerative scoliosis reconstruction using rhBMP-2 containing INFUSE® Bone Graft (Medtronic Spinal and Biologics, Memphis, TN) were studied (Table 1). For each case

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★ None of the other authors have disclosures to declare.

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Table 1
Surgical information for patients A, B, C and D.

Patient	Age, yrs	Study Aim	Surgery	Total BMP usage, mg	Total drain output, mL	Salvaged blood, mL
A ¹	58	Initial 'discovery' of BMP-2 drain leakage	T3–iliac PSF, L4–5 TLIF	16.2	2580	NA
B ²	65	Daily trend of BMP-2 drain leakage	T2–iliac PSF, L4–5, L5–S1 TLIF	12.0	2860	NA
C ³	68	Daily trend of BMP-2 leakage in salvaged blood	T6–S1 PSF, L4–5, L5–S1 TLIF	12.0	2500	870
D ³	71	Daily trend of BMP-2 leakage in salvaged blood	T10–iliac PSF, L3–4, L4–5, L5–S1 TLIF	12.0	1505	225

¹ Patient A: Single drainage sample analyzed on postoperative day (POD) 4.

² Patient B: Serial analysis performed on postoperative drainage. Final drain removal POD 10.

³ Patients C & D: Serial analysis performed on salvaged blood obtained after cell saver processing of postop drainage.

rhBMP-2 was prepared according to the manufacturer's instructions. Routine closure was performed over two Redivac suction drains placed deep to the fascia. Postoperative recovery in all four patients was unremarkable with good functional outcomes noted at follow-up.

Patients A and B were essentially the 'control' cases in our series. For patient A 16.2 mg of rhBMP-2 was used during the procedure and only a single drainage sample (500 mL) taken on POD 4 was sent for rhBMP-2 analysis. Since this was the first case in our series, our main aim was to 'discover' whether rhBMP-2 extravasates in surgical drainage. For patient B 12 mg of rhBMP-2 was used during surgery. For this case however a more robust charting and analysis of postoperative drainage were carried out. Drain output was closely monitored and drains were clamped once total output reached 300 mL for the day and were unclamped the following day. Each day the drain bottles were changed and the bottles containing the preceding day's output were sent for rhBMP-2 analysis. BMP-2 leakage trending was performed till POD 10 after which the surgical drains were removed.

For patient's C and D, 12 mg of rhBMP-2 was delivered during surgery. Post surgery the drains were connected to an OrthoPAT® cell saver (Orthopaedic Perioperative Autotransfusion System, Haemonetics Corporation, Braintree, MA) (Image 1). Portability of OrthoPAT® cell saver enabled the device to be linked to the drains even in the wards. Blood was salvaged daily from the drains and sent for rhBMP-2 analysis the same day.

The concentration of rhBMP-2 in postoperative drainage sample and salvaged blood was determined by enzyme-linked immunosorbent assay ELISA (Quantikine BMP-2, R&D Systems, Minneapolis, MN). A standard curve using serial dilutions of known concentration of rhBMP-2 (INFUSE, provided by Medtronic) in buffer was derived for each trial of ELISA as described in the product insert. The total leaked amount (mg) of rhBMP-2 was calculated from the concentration and volume. The leaked proportion (%) was calculated based on the initial amount used.

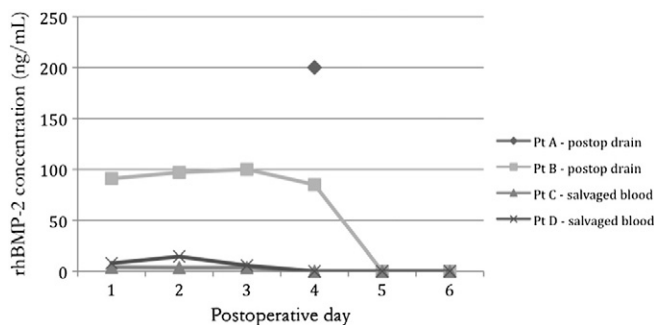


Fig. 1. Concentration of rhBMP-2 in postop drainage (patients A & B) and salvaged blood (patients C & D). Mean concentration of rhBMP-2 in drainage in patient B was 93.25 ng/mL (range 85–100). Mean concentrations in salvaged blood in patients C and D were 3.72 ng/mL (range 3.57–3.94) and 9.36 ng/mL (range 5.68–14.47), respectively.

Results

RhBMP-2 in postoperative drainage (patients A & B)

In patient A, 100 µg of rhBMP-2 at a concentration of 200 ng/mL was recovered from 500 mL of postoperative drainage on POD 4. Only a single sample was taken and no trending was performed. This represented 0.63% of the total amount implant. For patient B serial analysis of postoperative drainage showed rhBMP-2 leakage during the first four postoperative days. 136 µg of rhBMP-2 at an average concentration of 93.25 ng/mL leaked out during the first four days, representing 1.13% of the initial implanted amount (Table 2a). No rhBMP-2 was detected after POD 4.

RhBMP-2 in salvaged blood (patients C & D)

Compared to rhBMP-2 concentration in postoperative drainage in patients A & B, much lower concentrations (10-fold reduction) were detected in salvaged blood obtained after OrthoPAT® processing of postoperative drainage from patients C & D (Fig. 1). For patient C, 1.3 µg, 1.8 µg & 0.14 µg of rhBMP-2 were detected in salvaged blood on POD 1, 2 & 3 respectively, at an average concentration of 3.72 ng/mL. Total leakage proportion was 0.02%. In patient D, 1.2 µg, 0.7 µg and 0.01 µg

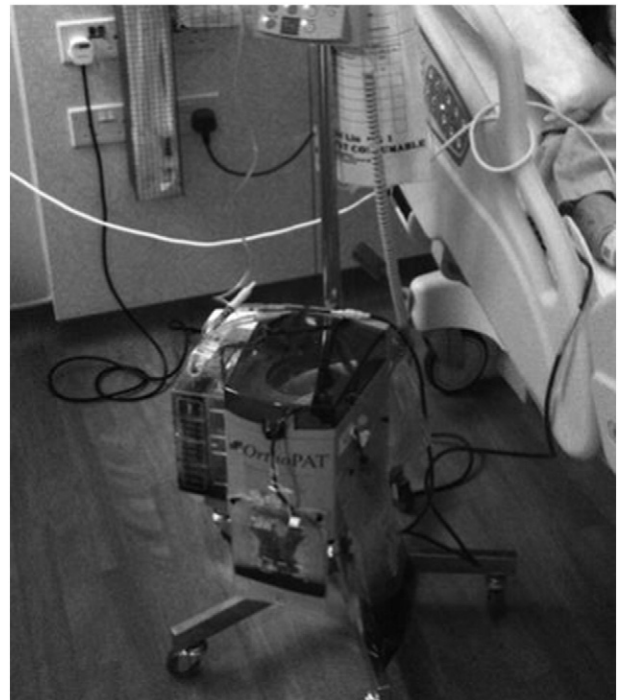


Image 1. Surgical drain connected to an OrthoPAT® cell saver.

Table 2a
RhBMP-2 leakage in postoperative drainage for patients A and B.

Patient	Total BMP usage, mg	BMP leak POD 1, µg	BMP leak POD 2, µg	BMP leak POD 3, µg	BMP leak POD 4, µg	BMP leak POD 5, µg	Mean BMP concentration, ng/mL	Total BMP leak, µg	Leak proportion ³ , %
A ¹	16.2				100		200		0.69
B ²	12	38.5	31.2	30.1	36.2	nil	93.25	136	1.13

¹ Patient A: Single drainage sample analyzed on postoperative day (POD) 4.

² Patient B: Serial analysis performed on postop drainage (no BMP detected after POD 4). Final drain removal POD 10.

³ Leakage proportion (total leaked amount/total BMP used) × 100.

were detected in salvaged blood after cell saver processing on POD 1, 2 and 3 (overall leakage proportion 0.01%). Mean concentration was 9.36 ng/mL (Table 2b).

Discussion

Cell Savers are widely used in spine surgery despite controversy regarding overall benefit [6,7]. The OrthoPAT® perioperative auto transfusion system is a cell saver designed specifically for use in orthopaedic procedures with significant blood loss such as joint replacement and spinal fusion. Red blood cells (RBC) are separated from waste products by centrifugation during both intraoperative and postoperative processing; they are then washed and re-concentrated for greater purity [8]. Portability of OrthoPAT® cell saver enables the device to be linked to the drains even in the wards.

Cell savers are deployed even in cases where rhBMP-2 is used for fusion augmentation. Mok et al. reported rhBMP-2 drain extravasation in a series of 9 cases of posterolateral fusion [5]. An average of 68 µg of BMP-2 (range, 13–498) was recovered from drains, representing 0.58% (range, 0.21%–4.2%) of the implanted amount. For our 'control' case (patient B) 135 µg of rhBMP-2 was recovered during the first four days after surgery, representing 1.13% of the total implanted amount. Results from our report complement the report of Mok et al. in demonstrating rhBMP-2 extravasation into surrounding field and eventually into postop drains. Perioperative cell salvage in this situation may lead to inadvertent systemic introduction of rhBMP-2. BMP-2 is inherently a proinflammatory molecule and systemic introduction may pose concerns. In rat models rhBMP-2 has shown to stimulate inflammatory cytokine production levels, with a dose dependent release of proinflammatory cytokines such as IL6, IL10 and TNF alpha [9].

Our study on patients C and D was to assess cell saver efficacy in filtering BMP. RhBMP-2 was still detectable in salvaged blood after drain contents underwent OrthoPAT® processing, though concentration was greatly reduced (10-fold reduction) when compared to rhBMP-2 recovery in patient B. The reduced rhBMP-2 concentration in salvaged blood could be attributed to OrthoPAT® processing. The molecules are either filtered away during centrifugation or degraded during RBC washing. Overall the reduced concentrations in salvaged blood do indicate cell saver efficacy in filtering rhBMP-2.

In our detection of rhBMP-2 in surgical drainage we have demonstrated BMP migration from the initial delivery site to operative field and drains. We have also demonstrated cell saver efficacy in filtering rhBMP-2 by noting reduced concentrations of rhBMP-2 in blood salvaged from postop drains.

Though our results appear to suggest minimal risk of rhBMP-2's systemic introduction due to cell saver filtering, our conclusions are limited by the small sample size and the fact that we were only able to analyze postop salvaged blood for rhBMP-2 presence. Intraoperative cell salvage is the more commonly deployed method of perioperative auto-transfusion and therefore rhBMP-2 analysis of blood recycled from operative field should be included in future projects. Further research is suggested to ascertain the true clinical application of cell saver filtration of rhBMP-2 and the overall safety of perioperative transfusion in these cases.

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Table 2b
RhBMP-2 detection in postoperative salvaged blood for patients C and D.

Patient	Total BMP usage, mg	BMP in salvage blood, POD 1, µg	BMP in salvage blood, POD 2, µg	BMP in salvage blood, POD 3, µg	BMP in salvage blood, POD 4, µg	BMP in salvage blood, POD 5, µg	Mean BMP concentration, ng/mL	Total BMP leak, µg	Leak proportion ² , %
C ¹	12	1.30	1.8	0.14	nil	nil	3.72	3.24	0.02
D ¹	12	1.20	0.7	0.01	nil	nil	9.36	1.91	0.01

¹ Patients C & D: Serial analysis performed on salvaged blood obtained after cell saver processing (BMP detected on POD 1–3).

² Leakage proportion (total leaked amount/total BMP used) × 100.