The impact of platelet-rich plasma on postoperative outcomes after spinal fusion: a systematic review and meta-analysis

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OBJECTIVE Platelet-rich plasma (PRP) is a biological agent obtained by centrifuging a sample of blood and retrieving a high concentration of platelets and plasma components. The concentrate is then stimulated for platelet secretion of various growth factors and cytokines. Although it is not widely used in clinical practice, its role in augmenting bony union among patients undergoing spinal fusion has been assessed in several clinical studies. The objective of this study was to perform a systematic review and meta-analysis of the existing literature to determine the efficacy of PRP use in spinal fusion procedures.

METHODS A comprehensive literature search was conducted using PubMed, Scopus, and EMBASE for studies from all available dates. From eligible studies, data regarding the fusion rate and method of assessing fusion, estimated blood loss (EBL), and baseline and final visual analog scale (VAS) scores were collected as the primary outcomes of interest. Patients were grouped by those undergoing spinal fusion with PRP and bone graft (PRP group) and those only with bone graft (graft-only group).

RESULTS The literature search resulted in 207 articles. Forty-five full-text articles were screened, of which 11 studies were included, resulting in a meta-analysis including 741 patients. Patients without PRP were more likely to have a successful fusion at the last follow-up compared with those with PRP in their bone grafts (OR 0.53, 95% CI 0.34–0.84; $p = 0.006$). There was no statistically significant difference with regard to change in VAS scores (OR 0.00, 95% CI –2.84 to 2.84; $p > 0.99$) or change in EBL (OR 3.67, 95% CI –67.13–74.48; $p = 0.92$) between the groups.

CONCLUSIONS This study found that the additional use of PRP was not associated with any significant improvement in patient-reported outcomes and was actually found to be associated with lower fusion rates compared with standard grafting techniques. Thus, PRP may have a limited role in augmenting spinal fusion.

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KEYWORDS PRP; platelet-rich plasma; bony union augmentation; autograft

Platelet-rich plasma (PRP) is a biological agent that is obtained by centrifuging a sample of typically autologous blood and retrieving a concentrate containing platelets and plasma components.¹ PRP contains a plethora of growth factors and cytokines through the secretions of platelets.^{2,3} Factors expressed by PRP were found to be involved in the growth of mostly connective tissue-related structures, raising the hypothesis that it will help in growth and regeneration of connective tissue, potentially within the musculoskeletal system. Following

the findings at the molecular level, PRP has been tested in various preclinical and translational studies for the treatment of musculoskeletal disorders and has shown a favorable potential.^{4,5}

Following clinical studies of PRP use in disorders such as osteoarthritis of the knee⁶ and plantar fasciitis,⁷ the first examples of PRP use in the spine were presented in the treatment of discogenic pain resulting from degenerative disc disease.^{8,9} Intradiscal PRP injections were found to be associated with significant reductions in back pain and

ABBREVIATIONS EBL = estimated blood loss; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MD = mean difference; NOS = Newcastle-Ottawa Scale; PRP = platelet-rich plasma; RCT = randomized controlled trial; VAS = visual analog scale.

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increased rates of return to work.¹⁰ However, a considerable proportion of patients with degenerative disc disease undergo surgical procedures, and spinal fusions stand out as one of the most frequently utilized treatment modalities.

Stemming from the previous experience, several studies have since presented their findings after using PRP in addition to allografts in spinal fusion procedures. To date, there is variability in the conclusions regarding the benefit of PRP administration. In light of this ambiguity, we aimed to perform a systematic review and meta-analysis of the existing literature to determine the efficacy of PRP use in spinal fusion procedures.

Methods

The guidelines used for this systematic review and meta-analysis were the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹¹

Search Strategy

A comprehensive literature search was conducted using PubMed, Scopus, and EMBASE for studies from all available dates. Two independent investigators (W.W. and A.T.E.) conducted the search and selected the studies. In addition, references of included studies were reviewed to identify additional articles. The following keywords were used for the search: platelet rich plasma, artificial growth factors, lumbar fusion, and lumbar surgery.

Selection Criteria

Studies were included only if they 1) were randomized controlled trials (RCTs) or observational studies that compared outcomes between patients undergoing spinal fusion with the use of PRP and those without it, 2) recorded outcomes of interest, and 3) were written in the English language. Duplicate studies were only included if their patient populations were different.

Data Extraction

The following variables were abstracted from the included studies: 1) first author and year of publication; 2) study design; 3) comparative groups, 4) patient demographics, including age, sex, and average follow-up time; 5) fusion rate and method of assessing fusion; 6) estimated blood loss (EBL); 7) operative time; and 8) baseline and final visual analog scale (VAS), Oswestry Disability Index, and SF-36 scores.

The meta-analysis was conducted on 3 variables: fusion rate, VAS scores, and EBL. Due to inconsistent reporting across all studies, other outcomes could not undergo meta-analysis.

Critical Appraisal

The quality of studies was assessed using the Newcastle-Ottawa Scale (NOS)¹² for observational studies and the Cochrane Collaboration's tool for assessing risk¹³ for RCTs. Confidence in the estimate of outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.¹⁴

Statistical Analysis

Categorical outcomes were summarized using odds ratios with 95% confidence intervals. Mean differences (MDs) were used to summarize continuous outcomes. The two groups that were being compared were those undergoing spinal fusion with PRP and graft (PRP group) and those with a graft only (graft-only group). Heterogeneity was represented with the Higgins I-square (I^2). A random-effects model was used when meta-analyses indicated greater than 50% heterogeneity.¹⁵ Pooled estimates and effect sizes were represented by forest plots, while funnel plots were used to indicate publication bias. Statistical analysis was conducted using Review Manager 5.3 (Cochrane Collaboration); $p < 0.05$ was considered significant.

Results

Search Results

Our literature search resulted in 207 articles. Forty-five full-text articles were screened, of which 11 studies were included for meta-analysis. Further information related to study selection is summarized in Fig. 1.

Description of Studies

Three articles were retrospective cohort studies,^{16–18} while 4 were nonrandomized, prospective studies,^{19–23} and 4 were RCTs.^{24–27} A total of 741 patients were included in this meta-analysis, most of whom underwent posterolateral interbody fusion. A description of included studies can be found in Table 1.

Fusion Rate

Ten studies, consisting of 691 patients, had available data to compare fusion rates between the two groups. Successful fusion at the last follow-up was seen in 249 (79.6%) of 313 patients in the PRP group and 338 (89.4%) of 378 patients in the graft group. Those without PRP were more likely to have a successful fusion than those with PRP in their bone grafts (OR 0.53, 95% CI 0.34–0.84; $p = 0.006$) (Fig. 2).

Visual Analog Scale

Five studies reported VAS scores; 86 patients were included in the PRP group and 96 patients were included in graft-only group. There was no statistically significant difference in change in VAS scores between the groups (MD 0.00, 95% CI –2.84 to 2.84; $p > 0.99$) (Fig. 3).

Estimated Blood Loss

Four studies recorded EBL (in mL), with 92 patients in the PRP group and 186 in the graft-only group. There was no statistically significant difference in change in EBL between the groups (MD 3.67, 95% CI –67.13 to 74.48; $p = 0.92$) (Fig. 4).

Quality of Included Studies and Bias Assessment

Publication bias was not evident based on funnel plots as shown in Supplemental Figs. 1–3. Observational studies showed high quality based on the NOS for observational

FIG. 1. PRISMA flowchart. Figure is available in color online only.

studies, where scores ranged from 5 to 8 of 8. Three studies did not contain adequate selection of a nonexposed cohort; these studies selected their control groups through historical chart reviews. More details can be seen in Table 2. RCTs also showed high quality of study design based on the Cochrane tool for assessing risk, with scores ranging from 6 to 8 as shown in Supplemental Fig. 4.

GRADE assessment indicated moderate quality of outcome reporting for EBL and VAS, while fusion rate was reported to have high quality. More can be seen in Table 3.

Discussion

This meta-analysis investigated the impact of PRP use on postsurgical outcomes for patients undergoing spinal fusion surgery. The results did not show any significant differences between PRP use and no PRP use with regard to VAS scores for pain (OR 0.00, 95% CI −2.84 to 2.84;

$p > 0.99$) and EBL (OR 3.67, 95% CI −67.13 to 74.48; $p = 0.92$). In terms of fusion rates, significantly higher rates were detected in patients who did not receive additional PRP compared with those in whom PRP was used (OR 0.53, 95% CI 0.34–0.84; $p = 0.006$).

Over the years, numerous additional products have been used to augment fusion and increase success in spinal fusion procedures.²⁴ Currently, the most commonly utilized products are allografts, autografts, and bone morphogenetic protein. Allografts have been shown to be a promising material to supplement the fusion process in multiple studies.^{28,29} However, allografts have been questioned in terms of efficacy and thought to have a lower success rate compared with autologous grafts.³⁰ In contrast, autografts have been used as the gold standard for long periods of time, with “excellent” results following the fusion procedure.^{31,32} Still, autografts had their own safety concerns, namely the donor site–related complications (especially

TABLE 1. Demographics and characteristics of included studies

Authors & Year	Study Design	Procedure	Group	Sample Size	Females (%)	Mean Age, Yrs	Mean Follow-Up Time, Mos	Fusion Assessment
Acebal-Cortina et al., 2011 ¹⁹	Prospective non-randomized	PLIF	PRP + autograft + hydroxyapatite	67	38 (56.7)	57.0	24	AP x-ray: continuous intertransverse mass
			Autograft + hydroxyapatite	40	16 (40)	59.0		
Carreon et al., 2005 ⁶	Retrospective	PLIF	PRP + autograft	76	36 (47.4)	50.6 (28–87)	32 (24–48)	CT: NA
			Autograft	76	36 (47.4)	49.9 (26–79)	37 (24–56)	
Hartmann et al., 2010 ²⁰	Prospective non-randomized	Anterior fusion (thoracic/lumbar)	PRP + autograft	15	5 (43.7)	33.3	8.33 (4–15)	CT: evaluated by 3 planes, adequate volume & density shown
			Autograft	20	7 (39.8)	35.0	12.5 (4–30)	
Hee et al., 2003 ²¹	Prospective non-randomized	TLIF	PRP + autograft	23	15 (65.2)	44.3	Minimum 24	X-ray: fusion was considered solid if the anterior interbody area was fused, if the 2 posterolateral areas were fused, or if all 3 areas were fused
			Autograft	111	69 (62.1)	47.7		
Jenis et al., 2006 ²²	Prospective non-randomized	Anterior-posterior interbody fusion	PRP + autograft	15	5 (33.3)	40.3 ± 7.5	24	CT at 6 mos: continuous bone formation btwn endplates; FE x-ray at 24 mos: lack of observable motion btwn spinous processes
			Autograft	22	8 (36.3)	41.4 ± 8.0		
Kubota et al., 2019 ²⁵	RCT	PLIF	PRP + autograft	25	10 (40.0)	65.1	24	CT: bridging bone remodeling occurring btwn adjacent vertebrae
			Autograft	25	11 (44.0)	65.3		
Kubota et al., 2018 ¹⁷	Retrospective	TLIF	PRP + autograft	11	5 (45.5)	59.4	24	CT: bridging bone remodeling occurring btwn adjacent vertebrae
			Autograft	9	5 (55.6)	63.3		
Rezende et al., 2017 ²⁶	RCT	PLIF	PRP + autograft	20	26 (65.0)	49.2	6	Molnar x-ray classification; ⁴² Glassman CT classification ⁴³
			Autograft	20				
Sys et al., 2011 ²⁷	RCT	PLIF	PRP + autograft	20	7 (35.0)	NA	24	X-ray: no motion on FE films & bridging trabecular bone was shown
			Autograft	20	7 (35.0)			
Tsai et al., 2009 ²³	RCT	PLIF	PRP + autograft + CaS + fibrin glue	34	23 (67.6)	59.8 (33–80)	28.5 (24–34.9)	X-ray, <5° of motion at index level, <2 mm translation; CT, presence of bridging bone
			Autograft + CaS	33	27 (81.8)	63.3 (40–94)	27.6 (24–35.5)	
Weiner & Walker, 2003 ¹⁸	Retrospective	Lumbar intertransverse fusion	PRP + autograft	32	19 (59.4)	61 (32–84)	12	AP & FE x-ray, continuous bone through transverse process to transverse process; FE shows no movement of fused level
			Autograft	27	16 (59.3)	56 (11–16)		

AP = anteroposterior; CaS = calcium sulfate; FE = flexion-extension; PLIF = posterolateral interbody fusion; TLIF = transposas lumbar interbody fusion.

FIG. 2. Forest plot depicting ORs of the fusion rate. M-H = Mantel-Haenszel. Figure is available in color online only.

with iliac crest bone graft), increased blood loss, and operative time.^{33,34}

To date, no specific guidelines have been put forward for selecting the number and choice of various grafts in different circumstances. Using both allograft and autograft is a common practice among spine surgeons. PRP has been recognized as a hybrid, having properties similar to both autografts and allografts. As an autologous product, it is similar to local bone grafts, or iliac crest bone graft, and its lack of a requirement for any secondary invasive procedures is similar to allografts. PRP is usually prepared first by separating red blood cells from whole blood, including plasma and platelets, by centrifugation. Then, it is centrifuged once more to extract more platelets and added to a specific plasma volume to produce a specific concentration. Additionally, different commer-

cially available systems include proprietary products to the platelets, such as prepared leukocytes or citrate, to improve the concentration and effect of PRP.³⁵ Although included studies have not reported significant complications, we did not detect any significant benefit of PRP in terms of patient-reported outcomes. This is a concerning finding since the use of an additional agent without any benefit may not be cost-efficient, but it only adds an average of \$155, according to Landi et al.³⁶ However, it only adds an additional 18 minutes to transforaminal interbody fusions, on average.³⁷ Moreover, fusion rates were found to be better in the group without PRP use, further questioning its use in these cases. A recent systematic review by Elder et al. concluded that although PRP may be a promising strategy as a supportive agent in spinal fusion, there is insufficient evidence to recommend its use in spinal fu-

FIG. 3. Forest plot depicting MDs of change in VAS scores. Figure is available in color online only.

FIG. 4. Forest plot depicting MDs of EBL. Figure is available in color online only.

TABLE 2. Newcastle-Ottawa Scale for Observational Studies

Authors & Year	Selection					Outcome		
	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts	Assessment of Outcome	Acceptable Length of Follow-Up	Adequacy of Follow-Up of Cohorts
Hee et al., 2003 ²¹	*	—†	*	*	*	*	*	*
Weiner & Walker, 2003 ¹⁸	*	—†	*	*	*	*	*	*
Carreon et al., 2005 ¹⁶	*	*	*	*	*	*	*	*
Jenis et al., 2006 ²²	*	*	*	*	*	*	*	*
Hartmann et al., 2010 ²⁰	—‡	—‡	*	*	*	*	—§	*
Acebal-Cortina et al., 2011 ¹⁹	*	*	*	*	*	*	*	*
Kubota et al., 2018 ¹⁷	*	*	*	*	*	*	*	*

* = criterion satisfied; — = criterion not satisfied.

† Control group was historical.

‡ Includes patients with fractures.

§ < 12 months of follow-up for exposed cohort.

TABLE 3. Grading of Recommendations Assessment, Development and Evaluation (GRADE)

No. of Studies	Design	Quality Assessment					Summary of Findings			
		Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	No. of Patients		Relative Effect (95% CI)	Quality Importance
							PRP + Graft	Graft Only		
EBL										
4	Observational & RCT	Not serious	Not serious	Not serious	Serious	None	92	186	MD 3.67 (–67.13 to 74.48)	Moderate Important
Fusion rate										
10	Observational & RCT	Not serious	Not serious	Not serious	Not serious	None	249/313	338/378	OR 0.53 (0.34 to 0.84)	High Critical
VAS										
5	Observational & RCT	Not serious	Serious*	Not serious	Not serious	None	86	96	MD 0.00 (–2.84 to 2.84)	Moderate Important

* Standard deviation was imputed for those that did not report them.

sion surgery.³⁵ This idea was relatively due to the heterogeneity of studies and supports the statistical findings we obtained in the present study.

Stem cells are other potential agents that have been hypothesized to provide additional benefit in patients undergoing surgical procedures.^{38,39} A study by Eastlack et al. showed significant improvements in Neck Disability Index, neck VAS, arm VAS, SF-12 physical component, and SF-12 mental component scores with the use of stem cell allografts compared with cadaver allograft use in patients undergoing anterior cervical discectomy and fusion.⁴⁰ A similar study was conducted for 61 patients undergoing extreme lateral interbody fusion in a single-arm prospective study, and a fusion rate of 90.2% was achieved at the end of the 1st-year follow-up.⁴¹ Taking the results of PRP studies into account, stem cells are reported to achieve better outcomes when compared with PRP use. Moreover, stem cells are suggested as replacements of allografts, while the use of PRP was mostly tested as a combination therapy with an autograft.

Limitations

This study has limitations. First, among 11 included studies, only 4 studies were RCTs with small variabilities in their study designs. However, funnel plots indicated minimal to no bias for nonrandomized studies, as shown in Supplemental Figs. 1–3. Second, although the majority of the procedures were posterior lumbar fusion procedures, inclusion of different approaches has a potential impact on the results. Based on the GRADE criteria in Table 3, however, our results show moderate to high impact. Third, included studies only covered lumbar fusions, which limits the generalizability of the findings to all spinal fusions. Fourth, the timing of fusion assessments was found to be heterogeneous among studies, but the follow-up times of 8 of 11 studies ranged from 24 to 32 months.

Conclusions

The present study evaluated the use of PRP as one of the alternative regenerative biological agents to promote bony union and improvement in patient-reported outcomes among patients undergoing spinal fusion. We found that the additional use of PRP is not associated with any significant improvement in patient-reported outcomes compared with the standard procedure and is associated with lower fusion rates. Therefore, PRP may have a limited role as a biological agent in spinal fusion.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Yolcu, Wahood, Eissa. Acquisition of data: Yolcu, Wahood, Eissa. Analysis and interpretation of data: Yolcu, Wahood, Alvi. Drafting the article: Yolcu, Wahood. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Bydon. Statistical analysis: Yolcu, Wahood. Administrative/technical/material support: Bydon. Study supervision: Bydon.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Figs. 1–4. <https://thejns.org/doi/suppl/10.3171/2020.3.SPINE2046>.

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