Blood hsCRP And PGE2 Content With Clinical Outcome Using Modified Fenestratio-Restorative Spinoplasty Better Than Lamonectomy-Fusion In Lumbar Stenosis

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Objective: *Modified Fenestration-Restorative Spinoplasty* (MFRS) technique is an alternative to lumbar stenosis treatment, providing the equal decompression comparing with laminectomy techniques, without the implant, less expensive and complication rates. The purpose of this study was to determine which technique gives better inflammation and clinical outcome based on *high sensitive C-Reactive Protein* biomarker (hsCRP) and *Prostaglandin E_2* (PGE_2), Visual Analog Scale (VAS) of the day 7th postsurgery and ODI scores 3rd month post surgery.
Methods: This study design is an experimental pretest-posttest randomized control group design.
Results: This study results showed that the mean levels of hsCRP day 7th postsurgery were differ significantly between MFRS (23,09 ± 15,3 mg/L) compared to LF (39,53 ± 24,4 mg/L). Likewise for the mean levels of PGE_2 day 7th postsurgery were differ significantly between MFRS (491,39 ± 528,5 pg/ml) compared to LF (1103,7 ± 1033,6 pg/ml) at the significance level of $p < 0.05$). MFRS clinical outcomes better than LF ($p < 0.05$), for means of VAS value day 7th postsurgery and ODI score 3rd month postsurgery. Perioperative variable analysis shows that MFRS was better than LF in: length of surgery, blood loss, postsurgery Hb and patient length of stay ($p<0,05$).
Conclusions: MFRS technique is an alternative technique of lumbar stenosis treatment better than the LF, in terms of improved levels of hsCRP and PGE2, leading to faster clinical outcomes improvement, less complications and lower costs. MFRS technique should be used as a treatment of lumbar stenosis.
Key words: lumbar stenosis, inflammatory biomarker, clinical outcome, MFRS and LF.

INTRODUCTION

Lumbar stenosis occurs due to degenerative lumbar spine, 1.7 to 8% prevalence reported in the general population, over the age of 60 years. The main complaint generally; lower back pain, neurogenic claudication, until motor, sensory and autonomic nerves disturbance,.[1-4] Laminectomy is the standard decompression method for lumbar stenosis.[5] While the weakness i.e extensive of tissues dissection, blood loss, and resection of posterior osteoligamen structures causing spinal instability.[6,7] To maintain the spine stability thus required spinal fusion. There are some risks that accompanied i.e. implant complications, postoperative pain, hospital inpatient and surgery cost increased up to 50%, plus the cost of the implant increased the total cost of up to 100% .[8-10]

At surgery, immune cells respond to tissue damage causing a local inflammatory, systemic response and pain.

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Sturmer et al. (2005) mention the severity of inflammation pain associated with concentrations of hsCRP.[11] Mechanisms of pain through several ways including up-regulation receptor cyclooxygenase-2 (COX-2) and increased production of PGE_2.[12-18] Swei-Ming et al. (2006) mention the mean patient length of stay after laminectomy in 34 patients were 10.1 + 2.8 days, only 14.7% able to ambulate the day after surgery.[19] Laminectomy modifications have been developed to bridge the weakness of the above procedure known as modified fenestration-restorative spinoplasty/MFRS. MFRS for decompression of the spinal canal as well as restoring the posterior osteoligament structure.[9] Issues raised in this study, is there any difference in the inflammatory response, pain response and postoperative clinical outcomes between MFRS than LF patients in lumbar stenosis. The main purpose of this study was to prove the inflammatory response, pain response and clinical outcomes of postoperative MFRS better than the LF in patients with lumbar stenosis.

MATERIALS AND METHODS

This study design was an experimental randomized control group pre and post-test design. In this study sought: (1) differences in blood levels of hsCRP and PGE2 (2) differences in clinical outcomes, a value of postoperative VAS and ODI after MFRS and LF surgery in lumbar stenosis patients. The study was conducted at Neurosurgery Department, Sanglah Hospital-Denpasar. Examination of CRP (high sensitivity) levels performed in the Prodia Clinical Laboratory-Denpasar and PGE_2 conducted at the Virology Laboratory Faculty of Veterinary Medicine-Udayana University. Determination of VAS scale and filling out of the ODI questionnaire by the patient conducted in Sanglah Hospital Surgical Clinic.

Target population were all adult patients who underwent surgery for lumbar stenosis in Neurosurgery Department, Sanglah Hospital. Sample selection and randomized subjects by permutted block random sampling technique, after meeting the inclusion and exclusion criteria. Number of sample calculation using Pocock formula resulting 20 samples of each group with total 40 samples and sample aged 40-70 years.[20]

The independent variables were the surgical techniques of MFRS and LF; dependent variables were the blood content of hsCRP and PGE_2, the VAS and ODI as clinical outcomes. Controlled variables were age, nutrition, level of surgery, ASA, and analgesic The experiment was conducted after obtaining approval (ethical clearance) from The Research Ethics Committee of the Faculty of Medicine, Udayana University.

Research Procedure

Laminectomy performed under general anesthesia with the patient in prone. Using midline skin incision in the lumbar region, based on C-arm guidance. Subperiosteal dissection to expose the lamina and facets join and laminectomy using Kerrison's rongeur including medial facet and foramina. If necessary discectomy performed for disc herniation until decompression achieved. [19,21] Based on the C-arm guidance, followed by insertion of pedicle screw with the appropriate size then appropriate size of the McSteffee plate fitted and the nut used to lock this system.[6,7,10,22,23]

MFRS has two stages, namely: trumpet laminectomy and spinoplasty. The first phase done as in the laminectomy to expose the lamina and cutting L-shaped spinous process then bend to caudal using Aesculap's high speed drill., continued by laminectomy, leaving just enough for spinoplasty. Widening of the medial facet and foramina with Kerrison rongeur. If necessary lumbar discectomy performed at the same time as laminectomy above and the adequacy of decompression is achieved when the duramater pulsation was visible. The second phase, which bent spinous process caudal returned to its original position anatomically, and attached to the cephalad using a nonabsorbable thread.[9]

Laboratory Examination

HsCRP examination conducted by the immunoturbidimetric method of Roche Diagnostic (USA).[24] PGE_2 xxamination conducted in accordance to standard procedures as Arborassay (USA).[25]

Clinical Outcome Examination

VAS assessment on the day before surgery, followed by 3rd and 7th postoperative day, based on the VAS line. ODI assessment on the day before surgery and 3 months postoperatively.[6,26]

Data Analysis

Descriptive characterization of the data subject. Test for normality and homogeneity of hsCRP, PGE_2, VAS and ODI data. Comparability of the pre-test MFRS and LF groups using nonparametric Mann-Whitney test ($\alpha = 0.05$). Analysis of the difference using Mann-Whitney and analysis of the mean difference between the measurements with Friedman and Wilcoxon test at $\alpha = 0.05$.

RESULTS

In this study, the mean age of patients in the operated group with MFRS technique were 55.35 ± 9.56 years and at LF group was 52.75 ± 9.7 years with age range of the two groups of 40-70 years (p>0.05). Patients sex as male and female were consecutively; in MFRS 15 (75%) and 5 (25%), whereas in the LF group were 13 (65%) and 7 (35%) (Table 1).

HsCRP Value Analysis

Normality of distribution using Shapiro-Wilk test at $\alpha = 0.05$, from the test observed that the majority of data were not normally distributed. In this study, preoperative hsCRP data in MFRS group were comparable to the LF group by p value > 0.05 (Table 2). In this study, there were significant differences in hsCRP between MFRS and LF on the day 7th after surgery ($p<0.05$). This suggests that the inflammatory MFRS show a statistically lower.

Results of PGE_2 Value Analysis

In this study, pre-operative PGE_2 data in MFRS group were comparable to the LF by p values> 0.05 and there were significant differences in PGE_2 between MFRS and LF on the day 7th after surgery ($p<0.05$) (Table 3).

Mean reduction of PGE_2 levels were not significant on day 3rd in both groups ($p> 0.05$), There were significant differences in the average

PGE_2 decreased in the MFRS group from preop to day 7th that reached 484.1 pg/ml (p = 0.03) while in the LF group increased 207.55 pg/ml by p = 0.681 (Table 4).

Table 1
Characteristic of research subject

Characteristic	Both Groups	MFRS	LF	p
Age (year)	54.05 ± 9.59	55.35 ± 9.56	52.75 ± 9.70	0.399
Sex:				
Male	28 (70 %)	15 (75 %)	13 (65 %)	0.490
Female	12 (30 %)	5 (25 %)	7 (35 %)	
Body Weight (kg)	66.35 ± 9.33	69.25 ± 9.71	63.45 ± 8.15	0.658
Height (cm)	166.63 ± 7.74	169.20 ± 7.80	164.05 ± 9.71	0.428
BMI	23.63 ± 2.17	23.92 ± 2.19	23.32 ± 2.16	0.389
Level :				
1 level	30 (75%)	14 (70%)	16 (80%)	0.465
2 level	10 (25%)	6 (30%)	4 (20%)	

Table 2
Means Difference of hsCRP pre-op, day 3rd and day 7th post-op between MFRS and LF

Examination	Means hsCRP (mg/L)		p value
	MFRS	LF	
Pre-op	8.16 ± 17.30	12.01 ± 20.60	0.277
Day 3rd Post-op	95.97 ± 57.10	108.89 ± 67.30	0.738
Day 7th Post-op	23.09 ± 15.30	39.53 ± 24.40	0.023

Table 3
Means Difference of PGE_2 pre-op, Day 3th and Day 7th post-op between MFRS and LF

Examination	Means PGE_2 (pg/ml)		p value
	MFRS	LF	
Pre-op	975.50 ± 1185.60	896.16 ± 978.00	0.883
Day 3rd Post-op	762.78 ± 717.20	866.45 ± 1049.50	0.968
Day 7th Post-op	491.39 ± 528.50	1103.70 ± 1033.60	0.033

Table 4
Means Difference of PGE_2 between examination timing of MFRS and LF

Pair difference	Means Difference PGE_2 (pg/ml)	p value
MFRS		
Pre-op – Day 3rd post-op	212.71 ± 1117.30	0.575
Pre-op – Day 7th post-op	484.10± 926.00	0.030
Day 3th – Day 7th post-op	271.39 ± 714.60	0.126
LF		
Pre-op – Day 3rd post-op	29.69± 1492.20	0.455
Pre-op – Day 7th post-op	-207.55± 1487.10	0.681
Day 3th – Day 7th post-op	-237.25 ±1288.40	0.332

Outcome

In this study, preoperative VAS and ODI data in MFRS group were comparable to the LF group by p value > 0.05 (Table 5). The mean value of VAS preoperative, day 3rd and day 7th postoperative obtained in the MFRS group were 7.15 ± 1.2, 3.0 ± 0.7 and 1.45 ± 0.5, respectively. Similarly, mean value of VAS preoperative, day 3rd and day 7th post-operative obtained in the LF group were 7.35 ± 1.1; 3.95± 0.7 and 3.35 ± 0.6, respectively. There was a mean difference in VAS values on day 3rd postoperative between the two groups with p value <0.05 (presented in Table 5).

Table 5.
Means Difference of VAS pre-op, Day 3rd and post-op between MFRS and LF

Examination	Means VAS		*p* value
	MFRS	LF	
Pre-op	7.15 ± 1.20	7.35 ± 1.10	0.565
Day 3rd post-op	3.00 ± 0.70	3.95 ± 0.70	0.001
Day 7th Post-op	1.45 ± 0.50	3.35 ± 0.60	0.000

Table 6.
Means Difference of ODI score pre-op and 3 months post-op between MFRS and LF

Examination	Means ODI (%)		*p*
	MFRS	LF	
Pre-op	53±16	55 ± 19	0.799
At 3 months Post-op	11± 8	19 ± 9	0.012

Table 7.
Perioperative Variables Analysis

Variable	All Groups	MFRS	LF	*p*
operating time (minute)	131.7±32.4	112.0 ± 28.3	151.5± 23.2	0.0001
length of incision (cm)	12.37 ± 2.03	11.85± 2.03	12.9 ± 1.94	0.118
amount of bleeding (ml)	226.8 ± 117.6	156.4 ±48.1	297.3± 125.1	0.0001
preoperative Hb (g/dl)	13.5±1.49	13.4± 1.5	13.6 ± 1.5	0.795
postoperative Hb (g/dl)	11.9±1.49	12.4 ± 1.6	11.4± 1.2	0.044
length of stay (hari)	6.5± 1.5	5.6 ± 1.5	7.4 ± 0.7	0.0001

The ODI score (%) pre-and postoperative in the group MFRS obtained sequentially by 53 ± 16 and 11 ± 8, respectively while the LF group gained 55 ± 19 and 19 ± 9. Decreased in the mean score of ODI on MFRS group obtained 42% compared to the LF group gained 36% ($p < 0.05$). There were significant differences between the mean postoperative ODI score between MFRS compared with LF groups (Table 6).

The perioperative variables analysis, such as: operating time, length of incision, amount of bleeding, preoperative Hb, postoperative Hb and length of stay, presented in Table 7. There were differences in operation time, amount of bleeding, postoperative Hb and length of stay, MFRS was better than LF ($p < 0.05$).

DISCUSSION

High Sensitive C-Reactive Protein (hsCRP) and Prostaglandin E_2 (PGE_2) in Lumbar Stenosis

In normal circumstances, the production of CRP through the induction of IL-6 and IL-1 on hepatic CRP expression via Janus Kinase signal transduction (JK) and via the JAK-STAT pathway.[27] In the process of acute inflammation, CRP levels increased dramatically mainly by an increase in plasma concentrations of IL-6 produced by macrophages so that CRP is used as a marker of inflammation.[28] Production of IL-1ß, IL-6 and COX-2 increased after tissue damage that amplify the inflammatory process.[29,30] The data in this study, in accorandce with Sturmer et al., 2005, there was a slight increased above the normal reference value (4 mg/L) CRP in adults, namely the group MFRS (17.34 ± 8.17 mg/L) and the LF group (12.01 ± 20.67 mg/L).[11] Mentioned, to indicate inflammation CRP level greater than 7 mg/L.[31] In the event of an acute tissue injury, such as lumbar stenosis decompression surgery, triggers induction of IL-6 and IL-1 by Janus Kinase earlier, thus resulting in increased hepatic secretion of CRP.[28] Meanwhile, no investigators reported specific levels of hsCRP in lumbar stenosis surgery, this study as the first data reported that the mean levels of hsCRP in the postoperative MFRS was 23.09 ± 15.31 mg/L and mean levels of hsCRP in the postoperative LF was 39.53 ± 24.43 mg/L. These data indicate a significant difference ($p < 0.05$) that MFRS produce less inflammation compared to LF.

Surgery produces a complex systemic response caused by increased plasma levels of PGE_2 and IL-6. Input PGE_2 signal activate neurons sensitivity to pain after surgery. Nociceptive fibre releasing polypeptide, such as the substantia P, which increases the production of PGE_2.[32] In the chronic back pain due to lumbar stenosis, in which chronic inflammation occured, basophils, mast cells and platelets release inflammatory mediators including increased levels of PGE_2. After surgical

decompression, improved nutrients flow to the nerves, decreased mechanical stress and decreased nerve swelling which expected to reduce of low back pain complaints and reduction of inflammatory mediators including decreased levels of PGE_2.[33]

Mean preoperative levels of PGE_2 obtained from this study were above the normal reference levels of PGE_2, at 95 pg/ml, the MFRS group was 975.5 pg/ml and the LF was 896.16 pg/ml.[34] This study presents the first data of the mean levels of PGE_2 postoperative lumbar stenosis that MFRS group was 491.39 pg/ml and the LF was 1103.7 pg/ml ($p < 0.05$). This suggested, that lower PGE_2 level in MFRS indicates lower sensitivity of pain compared to LF.

Differences between examination time of hsCRP and PGE_2 levels in the MFRS and LF groups

In this study, found a significant increase in mean hsCRP levels on day 3rd in the group of MFRS was 87.81 mg/L and the LF group was 96.88 mg/L ($p < 0.05$) and the mean reduction in hsCRP levels of the day 3rd to 7 days postoperatively in the group of MFRS was 72.88 mg/L and the LF was 69.36 mg/L ($p < 0.05$). There were also significant differences in mean increased levels of hsCRP in each group by 7 days postoperatively, the MFRS group increased 14.93 mg/L and LF group increased 27.52 mg/ L ($p < 0.05$). This can be explained that the surgery itself carries the impact of acute inflammation due to the amount of tissue damage ocurred while aiming to end the chronic inflammation caused by stenosis lumbalis.[14,35,36]

In this study, there were significant differences in the mean decreased PGE_2 levels from preoperative to 7 days postoperative level in MFRS group ($p = 0.03$), but not significant in LF group. When compared to the mean levels of PGE_2 7 days postoperatively between MFRS with the LF groups was also different with p value = 0.033 (Table 3 and 4). Although MFRS and LF groups are both aiming for lumbar stenosis decompression to end the chronic inflammatory process after day 3rd appeared differences in PGE_2 levels due to continous inflammatory respond induced in the LF group.[37, 38] Inflammation eventually lead to increased endogenous eicosanoid, including prostaglandin E_2.[39,40] Increased PGE_2 levels 7 days postoperatively in the LF group showed that there was an increased of pain mediators due to greater inflammation prolong the pain after surgery.

Clinical Outcome

No one has compared the clinical outcomes between the MFRS with the LF groups in lumbar stenosis. In this study, the value of preoperative VAS and ODI scores on MFRS group were comparable to the LF group (p value> 0.05). VAS values in the two treatment groups continued to decline on day 3rd and 7 days postoperatively. Pain after lumbar decompression surgery does not immediately disappear but decreased slowly because of the pain from the surgery as well. Correction of blood flow and nutrient supply to the lumbar nerve, loss of mechanical pressure on the nerves will reduce nerve sensitivity to pain.[33] On days 3rd and 7th postoperatively, VAS values were always lower in the MFRS group compared with LF, this suggests that the MFRS technique provide lower postoperative pain than the LF. There were significant differences in mean of ODI scores between the MFRS group, 3 months postoperatively, compared with the LF. Nerve decompression methods were relatively equal and nerve function improvement was not expected to differ, but the pain factor plays an important role in the patients disability assessment, in short-term. Pain-free patients must be able and willing to move and active, which stimulate blood flow to the extremities and stimulate overall healing.[41,42]

Nerve decompression surgery in lumbar stenosis cases carries two main things that is adequate decompression of spinal canal, foramina including lateral recess and maintaining sagittal balance for lumbar stability.[43] MFRS technique provide adequate decompression, as in the LF, and reconstruct the posterior structures as Spinoplasty.[9] Not so with the LF technique, provide adequate decompression of spinal canal but osteoligament posterior complex discarded. Instead, posterolateral fusion using pedicle screw (implant) at the same time. Greater inflammation caused by the amount of tissue damaged and the addition of implant placement, increased postoperative pain and reduction of lumbar motion segment. Additional muscle spasms or stiffness of the waist also occured in the short term. However, in long-term studies generally did not differ. [43,44]

In the LF group, there were 2 patients (10%) underwent repeated surgery, due to implant infection and implant fatigue, accordance to Mardjetko et al. (1994) in meta-analysis of 25 studies. The loss of motility, due to fusion of lumbar segments, to load a large loading on the implant so that the possibility of fracture of the implant can happen.[44] There was an infection caused by complications of pedicle screw installation in operation with the LF technique, with infection cases less than 1%. The tendency of inflammation or infection of the operation using the LF technique is one of the causes of increased levels of hsCRP which higher in the LF group.[43]

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