Original article

Efficacy of N-methyl-2pyrolidone-ethyl heptanoate (PLGA)-bupivacaine in situ forming system on radicular and low back pain relief following lumbar discectomy: A randomized clinical trial

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BACKGROUND: Lumbar disc herniation (LDH) is the most common surgical intervention of spine surgery. During few days of the operation, most patients experience worrying low back pain (LBP) and radicular leg pain (RLP). Applying liquid form of bupivacaine in the vicinity of surgical field could be effective on pain relief only for few hours after operation. **METHODS**: In a double-blind prospective randomized clinical trial on patients with single level lumbar disc herniation (LDH), we tried to show the efficacy of N-Methyl-2Pyrolidone-Ethyl heptanoate (PLGA)-bupivacaine on LBP and RLP of 38 patients with American Society of Anesthesiologists (ASA) physical status I, and aged 27-65 years old.At the end of operation, 1 cc of PLGA-bupivacaine or pure PLGA was inoculated at the vicinity of thecal sac and root. LBP and RLP were measured using McGill Pain Questionnaire and visual analogue scale (VAS), immediately after operation and then after 6, 12 and 24 hours as well as one week and one month. **RESULTS:** The mean pain severity of LBP in PLGA-bupivacaine group (A) and pure PLGA group (B) were 25.7 ± 2.8 and 30.6±5.8 ($p < 0.001$), one week after surgery and 23.1 ± 1.4 and 25.2±2 ($p < 0.002$), after two weeks, respectively. After 4 weeks of operation, the severity of LBP were 22.3 ± 1.6 and 22.9 ± 1 in two groups respectively ($p = 0.01$). Severity of RLP according to VAS, from preoperative intervention until one month later, did not show any significant differences between two groups before and up to the first week after operation. However, after the first week until the end of follow-up, group A showed better scores in VAS. **CONCLUSIONS:** Accordingly, application of bupivacaine-PLGA had significant effect on LBP especially two weeks after operation, but it did not have any additional positive effects on RLP.

KEYWORDS: N-Methyl-2Pyrolidone-Ethyl Heptanoate (PLGA), Lumbar Discectomy, Bupivacaine

BACKGROUND

Radicular leg pain (RLP) and low back pain (LBP) which exist and continue after surgical procedure, have been a great problem for patients and medical care providers. During the first month of surgery and especially after fourteen days, patients usually suffer LBP and RLP.

Although different methods and drugs had been offered to control RLP and LBP, but still no convinced way exists for pain relief. Bupivacaine as a local anesthetic drug, if applied in the vicinity of surgical field could be effective on RLP and LBP relief, but only for few hours after operation. The liquid form of bupivacaine disappears rapidly but if it is bound to slow releasing constituent, it could be effective for longer durations. Different drugs, methods and mixture have been introduced to increase releasing duration of bupivacaine with more or less successful outcomes. In our previous study, we decided to apply adipose tissue impregnated with bupivacaine that yielded positive results. [1] The use of epidural fat impregnated with bupivacaine has shown different results and complications and decision on its use is sometimes difficult for the neurosurgeons. In other studies, intraoperative administration of epidural methylprednisolone plus bupivacaine for postoperative pain control was also effective but still the problems of application of bupivacaine; the duration of its effect and the way it wash away very soon have not been solved.[2] Although bupivacaine infiltration during operation was effective on pain control but its effect has been challenging compared with that of intrathecal administration of opioids.[3] Other studies were effective or disappointing on different routes of bupivacaine administration on postoperative RLP or LBP.[2-4]

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In this study, we aimed to use bupivacaine attached to N-Methyl-2Pyrolidone-Ethyl Heptanoate (PLGA) which may increase the duration of analgesic effect of drug up to one month. Normally, the analgesic effects of bupivacaine continue only for 2 to 3 hours. It was tried to evaluate if in patients who were operated under spinal anesthesia, PLGA-bupivacaine increase the duration of analgesic effects and comfortableness during recovery period.

METHODS

This was a double-blind prospective randomized clinical trial on patients with single level lumbar disc herniation (LDH) who underwent surgery. Approval was obtained from the ethics committee of Isfahan University of Medical Sciences. Primarily we wanted to test sixty patients but ten of them did not have our criteria completely, eight of them refused to contribute in our study, finally Forty two patients with American Society of Anesthesiologists (ASA) physical status I, aged 27-65 years fulfilled inclusion criteria and were recruited in this study at Al-Zahra university hospital, Isfahan, Iran, in 2011. A written informed consent was obtained from all patients.

Subjects were randomly allocated to one of PLGA-bupivacaine group (A) or pure PLGA group (B) based on a simple randomization process using uniform random number algorithm to produce random numbers in the interval from 0.0 to 1.0. Four patients with neurological complication before or after surgical intervention or those that were not referred back were excluded.

The surgical technique for all patients was the same and consisted of fenestration lumbar discectomy and foraminotomy. At the end of operation, 1 cc of PLGA-bupivacaine or pure PLGA was inoculated at the vicinity of thecal sac and root. The concentration of bupivacaine that was applied at the field of surgery was 0.625 mg/dl. Patients were transferred to recovery room and then neurosurgical ward, where neurological examination was performed and the patients were examined until 24 hours when they were discharged from hospital. Pain was recorded by visual analogue scale (VAS) by our assistant of neurosurgery who was not informed about patients groupings, immediately after operation, 6, 12 and 24 hours after it and then after one week and one month. For RLP, VAS of pain recording was scored between zeros to ten so that zero was no pain at all and ten indicated the most severe pain the patient had ever experienced. For LBP, McGill Pain Questionnaire was applied so that the severity of LBP was adjusted to patient's signs and symptoms. The whole process of this study is summarized in a consort diagram in Figure 1.

Statistical analysis

Numerical values were presented as mean ± standard error. Repeated measure ANOVA was applied as the main statistical method for analyzing data.Within each group, comparisons at each follow up time points were tested using repeated contrasts and between groups comparisons were conducted using two independent samples t-test. All analyses were performed by SPSS 18.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Thirty-eight patients ASA physical status I aged 27-65 years with mean age of 40.3±10.2 years (group A: 42.9-9.7 years and group B: 43.6-11 years) were selected from surgical clinic of Al-Zahra university hospital in Isfahan, Iran.

Of 38 selected patients 15 (39.2%) subjects were female and 23 (60.8%) were male, 20 patients were in group A [13(65%) males and 7 (35 %) females] and group B included 18 patients [10 (55.6%) males and 8 (44.4%) females]. Initially, 42 patients were selected but 2 patients of control group (group B) were excluded, one because of thecal sac injury at the time of operation and the second one because of lost to follow up after one month. Two patients in groupA came back after 2 months for follow up which were also excluded. There was not any significant difference in two groups age ($p = 0.82$) and sex ($p = 0.55$).

LBP that was assessed by means of McGill score is presented in table 1 and figure 2. Severity of RLP according to VAS from preoperative intervention until one month later is shown in table 2 and figure 3. There were not any significant differences in RLP between two groups before and up to the first week after operation, but after the first week until the end of follow up, VAS was significantly better in the groupA. There was no RLP in groupA but in group B, mild RLP continued up to one month after surgical intervention. No statistically significant difference between two groups was seen on VAS for RLP ($p = 0.56$).

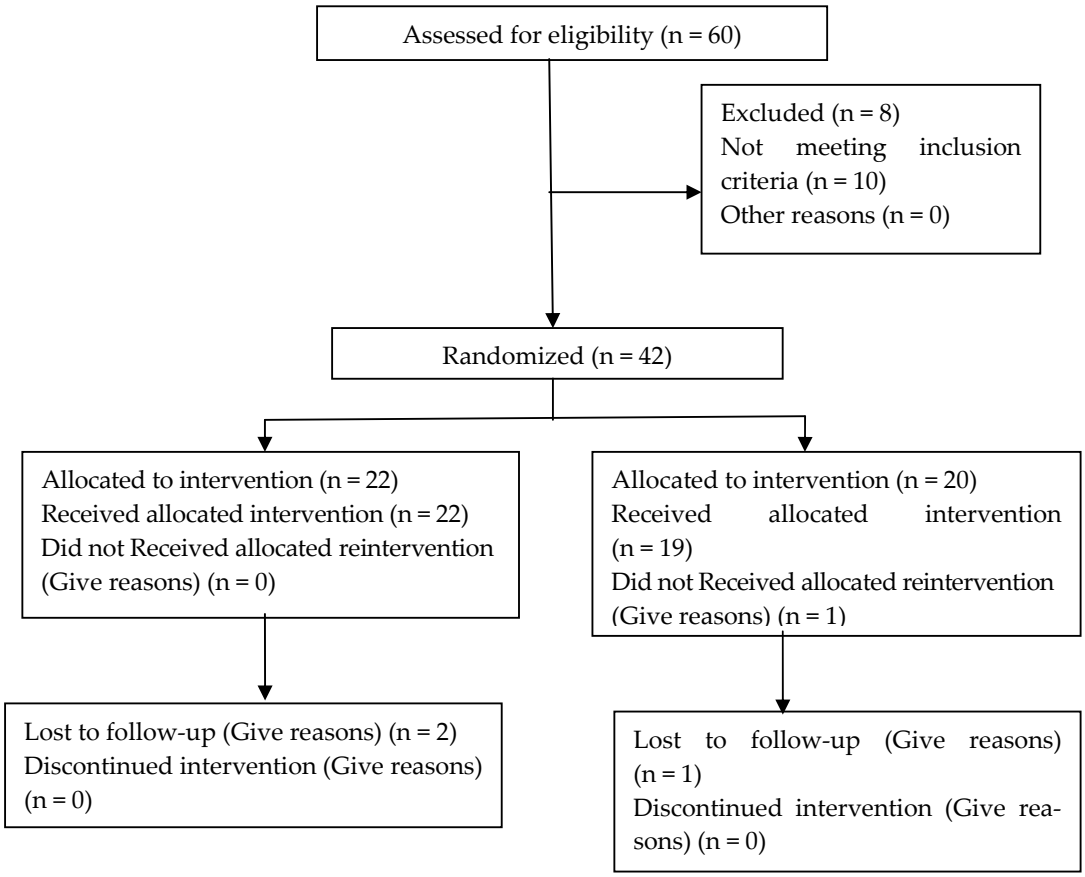

Figure 1: Flow diagram of the study

Table 1. Mean and standard deviation of low back pain score based on McGill pain score before operation and after it

	pure PLGA	PLGA-bupivacaine	p
Before operation	31.4 ± 4.7	31.7 ± 3.4	0.86
24 hours after operation	31.32 ± 4.28	31.1 ± 4.7	0.91
One week after operation	30.6 ± 5.8	25.7 ± 2.8	<0.01
Two weeks after operation	25.2 ± 2	23.1 ± 1.4	0.02
One month after operation	22.9 ± 1	22.3 ± 1.6	0.18
P-value among group	0.01	0.08	0.01

DISCUSSION

Post-operative LBP and RLP during first month of surgery and specially 7-14 days after operation is important factors that compromise surgical intervention for many patients. Despite different methods and designs that have been offered for pain control, the problem has not still been solved. [1,4,5] One of the challenging ways for pain control is applying analgesicsat the field of surgical operation.

Bupivacaine as an analgesic was applied in the surgical field for pain control with different results.[1,5] Because the liquid forms of drug wash away quickly, it was tried to bind bupivacaine with other matrixes or bases to increase the releasing time and re-absorption.[1,5] Normally, the analgesic effects of bupivacaine finish

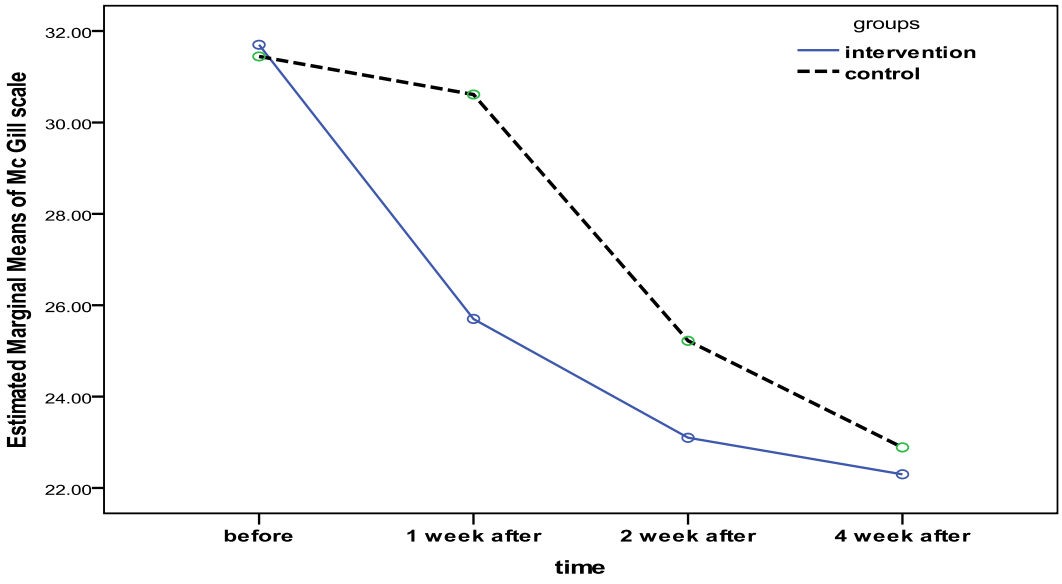

Figure 2. Low back pain score based on McGill pain score before operation and after it

Table 2. Mean and standard deviation of radicular leg pain score before operation and after it

	pure PLGA	PLGA-bupivacaine	p
Before operation	7.9 ± 2.8	8 ± 2.2	0.99
24 hours after operation	1.9 ± 2.8	1.9 ± 2.6	0.77
One week after operation	1.1 ± 1.6	0.55 ± 0.9	0.11
Two weeks after operation	0.47 ± 0.9	0.15 ± 0.4	0.17
One month after operation	0.24 ± 0.56	0	0.04
P-value among group	<0.001	<0.001	

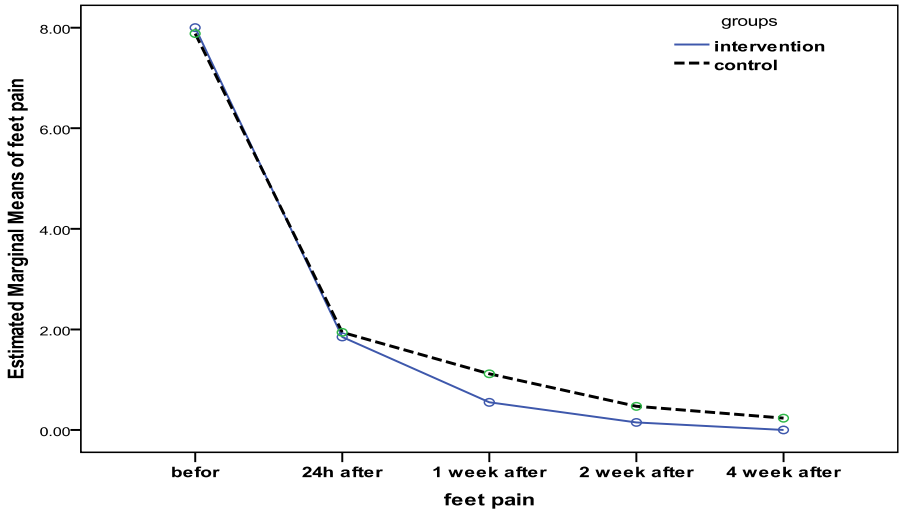

Figure 3. Radicular leg pain score before operation and after it

after 2 to 3 hours.[1,4]In this study we decided to use bupivacaine attached to N-Methyl-2Pyrolidone-Ethyl heptanoate (PLGA) that may cause duration of analgesic effect of drug be increased up to one month. PLGA not only acts as isolative material and could theoretically decrease the adhesion of surgical field in post-operative period but also could decrease the duration of re-absorption of bupivacaine up to one month.[6,7] PLGA or poly lactic-co-glycolic acid is a co-polymer which is used in a host of Food and Drug Administration (FDA) approved therapeutic devices, owing to its biodegradability and biocompatibility. PLGA is synthesized by random ring-opening co-polymerization of two different monomers, the cyclic dimmers (1, 4-dioxane-2, 5-diones) of glycolic acid and lactic acid.[1,4]

In our study, two groups (A and B) of patients consist of 20 cases were included, the mean age were 42.9 ± 9.7 and 43.6 ±11 years, respectively. Sothat the factors such as age and sex could not change the final results of our intervention. The sex distribution, education and employment status were also the same between groups.

In some studies the efficacy of bupivacaine was not seen, however, the application of bupivacaine or the maintenance dosage may have not been enough throughout the time. [2,5]

We used the same technique of operation for all of the patients and special details were considered to increase the chance of success. For example, PLGA was released at the vicinity of root and thecal sac as well as not using hemovac at the end of operation, which that could deplete PLGA. [1]In our previous experience, bupivacaine was applied in surgical field by adipose tissue. It may have not had enough concentration, at least for long duration of time.

Preoperative LBP according to McGill pain score in both intervention and control groups were so severe that decision for surgical intervention was made. Although the LBP and RLP decreased during the follow up period in both groups the same as other studies applying bupivacaine,[2,1] but the decreasing trend was not significantly different between two groups based on McGill pain score. Conversely, LBP and RLP showed significant differences between groups.

RLP in both groups decreased gradually during 4 weeks after operation according to VAS. Although there was no significant difference between groups, but after one week the pain amelioration was obvious so that none of the penitents in intervention group suffered from pain, although pain score was better in group during this period of time. RLP is caused by compression of disc material on nerve roots that will be treated after surgical resection of herniated disc material. Therefore, after operation the application of bupivacaine-PLGA does not have dramatic effects on RLP. On the other hand, LBP is the consequence of a chain of biochemical effects on free nerve ending that finally produces pain. In our experiences, bupivacaine-PLGA could theoretically diminish the pain severity during the first 4 weeks after operation.

In study of Geisler and Ross it was shown that following surgery, most ofpatients often suffer from RLP and LBP for a few days post-operatively and their pain gradually decreases, usually in the first days after surgery. [11, 12] Although in other studies, the application of PLGA was offered to reduction of post-operative fibrosis, [6,8] but our interest was the efficacy of PLGA on gradually absorption and releasing of bupivacaine.According to our data, the application of bupivacaine-PLGA had considerable effects on LBP especially after two weeks until the end of four weeks post-operatively. However, the outcome of bupivacaine-PLGA did not have any additional positive effects on RLP.

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