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Original Research Article

A comparative study of hemodynamic changes and adverse effects of intrathecal bupivacaine with fentanyl and intrathecal bupivacaine with clonidine in infra-umbilical abdominal and lower limb surgery

Krishna Prasad G. V., Vipin Jaishree Sharma*

Department of Anaesthesiology, MH Kirkee, Range Hills, Pune, Maharashtra, India

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***Correspondence:**
Dr. Vipin Jaishree Sharma,
E-mail: drkaypee99@yahoo.com

ABSTRACT

Background: Adjuvants prolong the action of intrathecal local anesthetic agents. They have shown to have significant analgesic effects in the postoperative period much after the regression of the sensory and motor blockade. Our objective of the current study was to compared the hemodynamic profile and adverse effects (nausea, pruritus, sedation and respiratory depression) in two groups of adult patients undergoing infra-umbilical and lower limb surgery under spinal anaesthesia using either intrathecal clonidine or intrathecal fentanyl as an adjuvant to intrathecal bupivacaine (0.5% heavy).
Methods: This randomized, prospective and observational study was undertaken in the Department of Anaesthesiology and Critical Care, 5 Airforce Hospital, Kanpur from the period of January 2014 to February 2016 on 120 patients fulfilling the inclusion criteria. Study patients were randomly allocated to the two groups Group I: Cases who received intrathecal 0.5% heavy bupivacaine (2.5 ml) + fentanyl (50 mcg/ml) (0.5 ml) (n=60 patients) and Group II: cases who received intrathecal 0.5% heavy bupivacaine (2.5 ml) + clonidine (60 mcg/ml) (0.5 ml) (n=60 patients).
Results: Mean age of patients in Group I and Group II was 42.60±5.93 and 42.03±7.16 years, respectively. Mean BMI of patients in Group I and Group II was 22.0±1.92 and 21.54±2.14 kg/m^2, respectively. Comparison of baseline hemodynamic parameters (heart rate (bpm), mean arterial pressure (mmhg), respiratory rate (/min) and oxygen saturation (%) did not show a significant difference between two groups.
Conclusions: With respect to the side effects like nausea and pruritus, these are significantly more in fentanyl group as compared to clonidine group.

Keywords: Bupivacaine, Clonidine, Infra-umbilical abdominal surgery, Lower limb surgery

INTRODUCTION

Management of post-operative pain in the infra-umbilical abdominal and lower limb surgeries increases patient satisfaction.[1] It also leads to earlier mobilization, shortens hospital stay, and reduces hospital costs. Additionally, the major goal in the management of postoperative pain is to minimize the dose of medications in view to reduce incidence of side effects while still providing adequate analgesia.[2]

Spinal anesthesia is the most common technique during infra-umbilical surgery.[3] Spinal anesthesia along with the local anesthetic agent displays relatively short duration of action which ultimately limits the type of surgeries to be performed under spinal anesthesia. The shorter action

duration also warrants the use of opioids and other drugs to provide post-operative analgesia.[4]

Over the years several studies have worked on different mechanisms to prolong the action of intrathecal local anesthetic agents with the help of adjuvants.[5-7] Different adjuvants like clonidine, dexmedetomidine, midazolam, opioids, neostigmine and magnesium sulphate have been studied to prolong the effect of spinal anaesthesia.[8-13] Additionally, they have been shown to have significant analgesic effects in the postoperative period much after the regression of the sensory and motor blockade thus ensuring post-operative pain relief and allowing early ambulation. Bupivacaine is a popular local anesthetic agent used for spinal anesthesia with duration of action of 60 to 240 minutes.[14,15] Various drugs have been used in the past as an adjuvant with bupivacaine to increase the efficacy and duration of the neuraxial blockade.[16,17] Opioids were the first group of drugs to be used as an adjuvant with bupivacaine. Use of opioids resulted in increased duration of analgesia but was associated with undesirable side effects like nausea, vomiting, respiratory depression and sedation. Fentanyl is a short acting lipophilic opioid, which binds to a family of G-protein-linked pre and postsynaptic opioid receptors in Laminae I and II of the dorsal horn of spinal cord. Fentanyl is the most frequently used intrathecal lipophilic opioid and when administered in single dose of 10-30 mcg it has rapid onset and short duration of action (4-6 hrs) with minimal cephalad spread.[18] Clonidine is an α_2-adrenergic agonist that is often administered intrathecally in humans. Clonidine has analgesic effect at spinal level mediated by postsynaptic α_2 adrenoreceptors in dorsal horn of spinal cord. Studies in rats have shown that intrathecal clonidine produces side effects like hypotension; bradycardia and sedation. Intrathecal clonidine can decrease sympathetic nervous system activity, renin-angiotensin levels and vasopressin release thereby reducing the tolerance to hemodynamic changes.[19]

Addition of clonidine as an adjuvant prolonged the bupivacaine spinal block.[20] However, the marked haemodynamic changes and sedation were observed which may limit the usefulness of intrathecal clonidine. Similarly, in few studies it was found that the intraoperative hypotension increased with the increasing doses of bupivacaine, however, when fentanyl was used as an adjuvant, both the incidence and severity of hypotension increased.[21,22]

With this background, the present study was proposed with an aim to compare the hemodynamic profile and adverse effects (nausea, pruritus, sedation and respiratory depression) in two groups of adult patients undergoing infra-umbilical surgery under spinal anaesthesia using either intrathecal clonidine or intrathecal fentanyl as an adjuvant to intrathecal bupivacaine (0.5% heavy).

METHODS

This randomized, prospective and observational study was undertaken in the Department of Anaesthesiology and Critical Care, 5 AirForce hospital, Kanpur. This study was carried out from the period of Jan 2014 to Feb 2016 in the patients scheduled for elective infra-umbilical abdominal and lower limb surgeries under spinal anesthesia. A total of 120 patients fulfilling the inclusion criteria were enrolled in the study and were randomly allocated to the two groups as follows:

Group I: Cases who received intrathecal 0.5% heavy bupivacaine (2.5 ml) + fentanyl (50 mcg/ml) (0.5 ml) (n=60 patients)

Group II: Cases who received intrathecal 0.5% heavy bupivacaine (2.5 ml) + clonidine (60 mcg/ml) (0.5 ml) (n=60 patients)

Inclusion criteria

All patients in the age group of 18 to 60 yrs, in ASA status I and II, who did not have any contraindication to spinal anaesthesia and scheduled for elective infraumbilical abdominal surgery in the study hospital were included in the study.

Exclusion criteria

All the patients less than 18 yrs of age and more than 60 yrs, or who have contraindication for spinal anesthesia, or suffering from hypertension and who had undergone obstetric surgery were excluded from the study.

After the approval from the Institutional Ethical Committee and obtaining the written informed consent from study participants, about 120 patients in the age group of 18 to 60 yrs, in ASA status I and II, scheduled for elective infraumbilical abdominal surgery under spinal anesthesia were enrolled for the study. They were randomized in two groups of 60 each (n=60) by a sealed envelope system. First group (Group I) received 2.5 ml of 0.5% bupivacaine (heavy) mixed with 25 mcg fentanyl & the second group (Group II) was administered 2.5 ml of 0.5% bupivacaine (heavy) mixed with 30 mcg clonidine.

All patients were advised to fast after 22:00 hours on previous night of surgery. They were premedicated with Tab Diazepam 5 mg orally, the night before surgery. In the operating room after attaching all essential monitors, (NIBP, pulse oxymeter and ECG) the baseline parameters were recorded. All patients were preloaded with RL/NS 10 ml/kg prior to giving spinal anesthesia. Anesthesia was given with patient in sitting position, using 25 G Quinckes needle with a midline approach in L3-L4 subarachnoid space and the patient was immediately placed in supine position after injecting the drug.

Data collection

The requisite parameters namely pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and oxygen saturation were recorded initially at 2 and 5 min after giving spinal anesthesia. After that parameters were recorded at intervals of 5 minutes for 30 minutes and then at intervals of 15 minutes till the end of surgery. A decrease in systolic blood pressure more than 20% of basal reading was considered as hypotension and managed with intravenous crystalloid and injection mephenteramine 06 mg intravenously. A fall in heart rate less than 20% of basal reading was considered as bradycardia and managed with injection atropine 0.6 mg intravenously. A decrease in oxygen saturation less than 90% on room air and respiratory rate of less than 10 per min was considered as respiratory depression and managed by oxygen @ 5 l/min by face mask.

Data analysis

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 15.0 statistical analysis software. The values were represented in number (%) and Mean±SD.

RESULTS

All patients (n=120) completed the study; and were grouped as shown in Table 1.

There was no statistical difference in patients' age and anthropometry as shown in Table 2.

Table 1: Group wise distribution of cases.

Sr. no.	Group	Description	No. of cases	Percentage (%)
1.	I	Cases who received intrathecal bupivacaine with fentanyl	60	50
2.	II	Cases who received intrathecal bupivacaine with clonidine	60	50

Table 2: Comparison of age and anthropometry of patients in two groups.

Sr. no.	Variable	Group I (n=60)		Group II (n=60)		Significance of difference	
		Mean	SD	Mean	SD	"t"	P value
1.	Age (in years)	42.60	5.93	42.03	7.16	0.472	0.638
2.	Body weight (kg)	58.45	6.55	58.77	6.97	-0.256	0.798
3.	Height (cm)	163.05	9.21	165.23	8.74	-1.332	0.185
4.	BMI (kg/m^2)	22.00	1.92	21.54	2.14	1.248	0.215

Table 3: Comparison of baseline hemodynamic parameters between groups.

Sr. no.	Variable	Group I (n=60)		Group II (n=60)		Significance of difference	
		Mean	SD	Mean	SD	"t"	P value
1.	Heart rate (bpm)	77.23	11.24	80.82	12.28	-1.668	0.098
2.	Mean arterial pressure (mmHg)	94.42	10.19	91.43	10.45	1.583	0.116
3.	Respiratory rate (/min)	17.05	3.08	17.10	2.96	-0.091	0.928
4.	Oxygen saturation (%)	98.97	0.99	98.92	1.00	0.276	0.783

The age and anthropometry data reveal that the age of patients included in our study ranged from 31 to 57 years. Mean age of patients in Group I was 42.60±5.93 (range 31-54 years) years as compared to 42.03±7.16 (range 31-57 years) years in Group II. On comparing the data statistically the difference between two groups was not found to be significant statistically (p=0.638). Body weight of study patients ranged from 47 to 72 kg. Mean body weight of patients in Group I was 58.45±6.55 (range 49-70) kg as compared to 58.77±6.97 (range 47-72) kg in Group II. On comparing the data statistically, this difference was not found to be significant (p=0.798). Height of patients involved in the study ranged from 145 to 180 cm. Mean height of patients in Group I was 163.05±9.21 (range 145-180) cm as compared to 165.23±8.74 (range 148-180) cm in Group II. On comparing the data statistically, this difference was not found to be significant (p=0.185). Also, the BMI of study patients ranged from 17.2 to 26.6 kg/m^2. Mean BMI of patients in Group I was 22.0±1.92 (range 18.6-26.2) kg/m^2 as compared to 21.54±2.14 (range 17.2-26.6) kg/m^2 in Group II. On comparing the data statistically, this difference was not found to be significant (p=0.215).

The baseline hemodynamic parameters were compared between the two study groups as shown in Table 3.

According to Table 3, heart rate of patients in Group I was 77.23±11.24 bpm as compared to 80.82±12.28 bpm in Group II. On evaluating the data statistically, this difference was not found to be significant (p=0.098). The mean arterial pressure of patients in Group I was

94.42±10.19 whereas the same in Group II was 91.43±10.45 mm of Hg. Though, mean blood pressure of patients in Group II was lower as compared to that in Group I yet this difference was not significant statistically (p=0.116). The mean respiratory rate of patients in Group I was 17.05±3.08 as compared to 17.10±2.96 in Group II. Statistically, the difference between the two groups were not significant (p=0.928). Finally, the mean oxygen saturation values in Groups I and II were 98.97±0.99 and 98.92±1.00% respectively, thus showing the difference between two groups not to be significant statistically (p=0.783). Overall, at the baseline, the two study groups did not show a significant difference for any of the baseline hemodynamic parameters.

Table 4: Comparison of heart rate at different time intervals between groups.

Sr. no.	Time interval	Group I (n=60)			Group II (n=60)			Significance of difference	
		N	Mean	SD	N	Mean	SD	"t"	P value
1.	Baseline	60	77.23	11.24	60	80.82	12.28	-1.668	0.098
2.	2 min	60	74.92	10.28	60	80.35	12.12	-2.648	0.009
3.	5 min	60	71.92	9.73	60	79.27	9.77	-4.131	<0.001
4.	10 min	60	70.32	9.51	60	75.10	10.66	-2.594	0.011
5.	15 min	60	67.37	9.48	60	71.88	9.97	-2.542	0.012
6.	20 min	60	66.15	9.09	60	70.63	10.53	-2.496	0.014
7.	25 min	60	64.77	9.04	60	70.87	9.08	-3.688	<0.001
8.	30 min	60	64.07	9.19	60	71.00	9.33	-4.102	<0.001
9.	45 min	60	63.63	8.25	60	70.03	8.54	-4.176	<0.001
10.	60 min	60	63.78	8.77	60	69.98	8.88	-3.848	<0.001
11.	75 min	54	64.83	7.91	58	70.62	9.17	3.565	0.001
12.	90 min	19	60.74	6.38	18	73.06	7.90	5.233	<0.001

Table 5: Comparison of mean arterial pressure at different time intervals between groups

Sr. no.	Time interval	Group I (n=60)			Group II (n=60)			Significance of difference	
		N	Mean	SD	N	Mean	SD	"t"	P value
1.	Baseline	60	94.42	10.19	60	91.43	10.45	1.583	0.116
2.	2 min	60	92.42	9.32	60	89.85	9.17	1.521	0.131
3.	5 min	60	89.97	8.58	60	86.65	9.91	1.960	0.052
4.	10 min	60	87.08	7.78	60	84.63	10.13	1.486	0.140
5.	15 min	60	84.58	6.91	60	82.97	9.53	1.064	0.290
6.	20 min	60	82.48	6.45	60	82.48	8.41	0.000	1.000
7.	25 min	60	81.73	6.24	60	82.27	7.50	-0.424	0.673
8.	30 min	60	81.22	6.48	60	82.72	6.57	-1.260	0.210
9.	45 min	60	81.28	6.42	60	82.47	5.55	-1.080	0.282
10.	60 min	60	81.65	5.63	60	83.37	5.49	-1.691	0.094
11.	75 min	53	81.68	5.46	55	84.44	5.30	-2.664	0.009
12.	90 min	19	84.60	6.55	18	84.28	4.80	0.171	0.865

Table 6: Comparison of respiratory rate at different time intervals between groups

Sr. no.	Time interval	Group I (n=60)			Group II (n=60)			Significance of difference	
		N	Mean	SD	N	Mean	SD	"t"	P value
1.	Baseline	60	17.05	3.08	60	17.10	2.96	-0.091	0.928
2.	5 min	60	16.78	2.98	60	17.17	2.94	-0.710	0.479
3.	10 min	60	16.73	2.60	60	17.40	3.14	-1.267	0.208
4.	15 min	60	16.28	2.18	60	17.12	2.96	-1.757	0.082
5.	30 min	60	15.85	2.48	60	16.80	2.96	-1.904	0.059
6.	45 min	60	16.73	2.79	60	16.80	1.88	-0.154	0.878
7.	60 min	60	16.07	2.26	60	16.63	1.81	-1.514	0.133
8.	75 min	60	15.97	1.87	60	16.53	2.09	-1.567	0.120
9.	90 min	19	15.74	2.33	18	16.89	1.45	-1.794	0.082

Apart from the baseline hemodynamic parameters, our study also recorded heart rate, mean arterial pressure, mean respiratory rate and mean oxygen saturation values at different time intervals between the study groups. According to Table 4, the heart rate at different time intervals between groups was calculated. As per the below Table 4, the mean heart rate values in Group II were higher as compared to that in Group I. Although, at baseline, the two groups were matched for mean heart rate and did not show a statistically significant difference (p=0.098), however, from 2 min interval onwards the difference between the two groups was significant statistically (p<0.05). At 90 min, mean heart rate in Group I was 60.74±6.38 bpm as compared to 72.00±8.22 bpm in Group II, thus showing a mean difference of 11.26 bpm between the two groups. Statistically, this difference was significant (p<0.001).

Table 5 reported a decline in mean arterial pressure from the 2 min post-intervention interval in both the study groups. The decline in mean arterial pressure continued in both the groups. At none of the time intervals except at 75 min interval, a significant difference between the two groups was observed.

Table 6 reveal that in Group I at all the subsequent time intervals, the mean respiratory rate was lower than baseline at all the subsequent intervals, whereas in Group II mean respiratory rate showed an increase which remained till 15 min interval. Thereafter, all the mean values in both the groups were lower than baseline values. On comparing the two groups, statistically no significant difference was observed between the two groups at any of the time intervals (p>0.05).

Table 7 suggest that throughout the study procedure; the mean oxygen saturation was above 98% in both the groups. Statistically, no significant difference between the two groups was observed at any time interval (p>0.05).

Table 7: Comparison of oxygen saturation at different time intervals between groups

Sr. no	Time interval	Group I (n=60)			Group II (n=60)			Significance of difference	
		N	Mean	SD	N	Mean	SD	"t"	P value
1.	Baseline	60	98.97	0.99	60	98.92	1.00	0.276	0.783
2.	5 min	60	99.07	0.92	60	99.05	0.87	0.102	0.919
3.	10 min	60	98.68	1.16	60	98.83	1.06	-0.740	0.461
4.	15 min	60	98.90	1.08	60	98.97	0.88	-0.369	0.713
5.	30 min	60	98.95	0.93	60	99.05	0.75	-0.650	0.517
6.	45 min	60	98.97	0.78	60	99.22	0.76	-1.776	0.078
7.	60 min	60	99.08	0.74	60	99.30	0.50	-1.877	0.063
8.	75 min	60	99.27	0.82	60	99.30	0.62	-0.251	0.802
9.	90 min	18	99.28	1.02	18	99.44	0.51	-0.621	0.539

Table 8: Comparison of two groups for the sedation score

Sr. no	Score	Group I (n=60)		Group II (n=60)	
		No.	%	No.	%
1.	2	59	98.3	58	96.7
2.	3	1	1.7	2	3.3

χ^2=0.342 (df=1); p=0.559 (NS)

Table 9: Comparison of two groups for side effects.

Sr. no	Complication	Group I (n=60)		Group II (n=60)		Significance of difference	
		No.	%	No.	%	χ^2	P value
1.	Hypotension	8	13.3	5	8.3	0.776	0.378
2.	Bradycardia	2	3.3	3	5.0	0.209	0.648
3.	Nausea	7	11.7	0	0	7.434	0.006
4.	Pruritus	8	13.3	0	0	8.571	0.003

In the Table 8, except for 1 (1.7%) patient in Group I and 2 (3.3%) patients in Group II, all the other patients had sedation score of 2. Statistically, the difference between the two groups was not significant (p=0.559).

The current study compared the number of side effects between two study groups (Table 9). Among the side effects, hypotension was the most common complication (n=13) followed by pruritus (n=8) and nausea (n=7). Bradycardia was observed in 5 cases only. In Group I, the complications like hypotension, pruritus, nausea and bradycardia were reported in 8 (13.3%), 8 (13.3%), 7 (11.7%) and 2 (3.3%) patients respectively. Whereas, in Group II; none of the patients had nausea and pruritus.

Hypotension was reported in 5 (8.3%) and bradycardia in 3 (5%) patients only. Statistically no significant difference between the two groups was observed with respect to complications like hypotension and bradycardia. However, pruritus and nausea were significantly higher in Group I as compared to Group II ($p<0.05$).

DISCUSSION

The aim of the present study was to compare the hemodynamic changes caused by intrathecal 0.5% bupivacaine (heavy) mixed with fentanyl (Group I) and intrathecal 0.5% bupivacaine (heavy) mixed with clonidine (Group II) and also to study the other side effects like nausea, pruritus, sedation and respiratory depression. For this purpose, a total of 120 patients in ASA status I/II scheduled for elective infraumbilical surgery under spinal anesthesia were enrolled in this study. They were randomly allocated to one of two groups of 60 patients each. Patients in Group I received intrathecal 0.5% hyperbaric bupivacaine 2.5 ml with fentanyl (25 mcg) and patient in Group II received intrathecal 0.5% hyperbaric bupivacaine with clonidine (30 mcg).

The two groups had a similar age and anthropometric profile thus indicating that these parameters did not have a confounding effect on the performance of trial drugs. Statistically significant decrease in mean arterial pressure and heart rate was observed in both groups. With respect to clinically significant hemodynamic events like hypotension and bradycardia, they were reported in 8 (13.3%) and 2 (3.3%) patients of fentanyl group and 5 (8.3%) and 3 (5%) patients of clonidine group, thus showing statistically no significant difference between the two groups ($p>0.05$).

The reason for lower prevalence of hypotension in clonidine group in present study could be the use of optimum dose of clonidine. The dose of 30 mcg in present study is close to the optimum dose of 37.5 mcg to produce effective analgesia without inducing hypotension when administered as adjuvant intrathecally.[23] Relatively lower adjuvant dosages of clonidine have been reported to cause fewer events of hypotension.[24] In comparison to the present study, few studies used 50 mcg and 75 mcg adjuvant dosages of clonidine found though higher yet statistically not significant difference in hypotensive events as compared to fentanyl 25 mcg.[25,26] In all these studies, the bradycardia was a less common side effect as also observed in present study and did not pose a significant difference between the two groups. These findings as such indicate that adjuvant use of clonidine with respect to hypotensive events is dose-dependent, however, at varied dosages being used currently, the frequency of hypotensive events are similar to that of fentanyl.

In the present study, except for nominal changes in respiratory rate, the respiratory rate remained almost stable throughout the study period. The mean oxygen saturation also remained above 98% in both the groups at all the time intervals, showing no statistically significant difference between two groups. No case of respiratory depression was reported in either of the two Groups. Intrathecal use of low dose clonidine and fentanyl as adjuvant to bupivacaine has not been shown to be associated with respiratory depression in literature.[26-32] Thus, the findings in this present study indicated a safe ventilatory profile of both drugs which did not end up in a respiratory depression and is consistent with the findings reported in literature. Although a few case reports describes respiratory depression after intrathecal fentanyl (after 100 mcg of epidural fentanyl) yet its use in low-dosage as an adjuvant to bupivacaine is relatively safe and rarely ends up in respiratory depression.[33]

In the present study, statistically no significant difference in sedation scores of patients in the two groups was observed. However, one study reported achievement of sedation in 88% of cases in clonidine group as compared to only 12% of cases in fentanyl group, however, in their study fentanyl was used at a relatively lower dosage (15 mcg) whereas in present study this dose was 25 mcg.[34] Similar to our study, using a similar adjuvant dose of fentanyl and clonidine but using a different scale to measure sedation (De Kock sedation scale), another study reported achievement of same score (score-1) in both the groups.[24] One study report of no excessive sedation at 30 mcg clonidine.[35] Overall, these findings suggest that as far as sedation is concerned both the drugs at the given dosage are comparable.

Opioid use is commonly associated with side effects such as nausea and vomiting.[36] Low dose fentanyl added to Bupivacaine in spinal anesthesia is associated with fewer episodes of nausea and vomiting.[37] In the present study, nausea was noted only in patients receiving intrathecal fentanyl. No patient in clonidine group had complained of nausea. Similar results were also reported in one study who reported significantly higher prevalence of nausea in fentanyl group as compared to clonidine group.[25]

Intrathecal fentanyl frequently produces pruritus which is unfortunately difficult to prevent even by prophylactic medication.[38] The incidence of pruritus has been reported to be as high as 52% when 50 mcg fentanyl was used as adjuvant to 0.125% bupivacaine.[39] In the present study, pruritus was noted only in fentanyl group. Few studies have reported high incidence of pruritus in fentanyl group compared to clonidine group.[25,40]

CONCLUSION

On the basis of finding of this study it can be concluded that both adjuvants at given dosages with bupivacaine have similar hemodynamic profile. With respect to other side effects like nausea and pruritus, these are significantly more in fentanyl group as compared to clonidine group.

Recommendations

With respect to other adverse effects like pruritus and nausea, which were significantly more in fentanyl group as compared to clonidine group, clonidine 30 mcg seems to be an attractive alternative to fentanyl 25 mcg as an adjuvant to bupivacaine (0.5% heavy) in spinal anesthesia.

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