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右美托咪定复合曲马多超前镇痛对骨关节置换术患者镇痛效果、血流动力学及认知功能的影响*

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摘要 目的:探讨右美托咪定复合曲马多超前镇痛对骨关节置换术患者镇痛效果、血流动力学及认知功能的影响。**方法:**选取 2015 年 2 月~2018 年 12 月期间武警陕西省总队医院收治的行骨关节置换术患者 121 例,根据数表法将患者随机分为对照组(n=60)和研究组(n=61),其中对照组给予曲马多超前镇痛,研究组在对照组的基础上联合右美托咪定,比较两组患者镇痛效果、血流动力学指标及认知功能,记录两组手术期间不良反应发生情况。**结果:**研究组术后 4 h(T₂)、术后 8 h(T₃)、术后 12 h(T₄)、术后 24 h(T₅)时间点视觉模拟评分(VAS)低于对照组($P<0.05$)。研究组 T₂~T₅ 时间点心率(HR)、平均动脉压(MAP)低于对照组,血氧饱和度(SPO₂)则高于对照组($P<0.05$)。研究组术后 3 d、术后 1 周简易精神状态量表(MMSE)评分较对照组升高,中枢神经特异蛋白(S100β)水平则低于对照组($P<0.05$)。两组不良反应总发生率比较无差异($P>0.05$)。**结论:**骨关节置换术患者给予右美托咪定复合曲马多超前镇痛,镇痛效果确切,可有效维持血流动力学稳定,且对机体认知功能影响较轻,不增加不良反应发生率,临床应用价值较高。

关键词:右美托咪定;曲马多;超前镇痛;骨关节置换术;血流动力学;认知功能

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Effect of of Preemptive Analgesia with Dexmedetomidine and Tramadol on Pain Relief, Hemodynamics and Cognitive Function in Osteoarthroplasty Patients*

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ABSTRACT Objective: To investigate the effect of preemptive analgesia with dexmedetomidine and tramadol on pain relief, hemodynamics and cognitive function in osteoarthroplasty patients. **Methods:** 121 cases of osteoarthroplasty in Shaanxi Provincial Armed Police Corps Hospital from February 2015 to December 2018 were selected, which were randomly divided into control group (n=60) and research group (n=61) according to the number table method. The control group was given tramadol for preemptive analgesia, and the research group was combined with dexmedetomidine on the basis of the control group. The analgesic effect, hemodynamics and cognitive function of the two groups were compared, the occurrence of adverse reactions in two groups during operation were recorded. **Results:** Visual Analogue Scale (VAS) scores at 4 h (T₂), 8 h (T₃), 12 h (T₄) and 24 h (T₅) time point after operation in the study group were lower than that in the control group ($P<0.05$). Heart rate (HR) was lower in the study group than that in the control group at T₂-T₅ time point, while blood oxygen saturation(SPO₂) in the study group was lower than that in the control group, and mean arterial pressure (MAP) was higher than that in the control group($P<0.05$). Simple Mental State Scale (MMSE) scores in the study group were higher than those in the control group at 3 d after operation and 1 week after operation, while central nervous specific protein (S100β) scores were lower than those in the control group ($P<0.05$). There was no difference in the total incidence of adverse reactions between the two groups($P>0.05$). **Conclusion:** Preemptive analgesia with dexmedetomidine combined with tramadol has definite analgesic effect in osteoarthroplasty patients, which can effectively maintain hemodynamic stability with little effect on cognitive function, and does not increase the incidence of adverse reactions. It has high clinical application value.

Key words: Dexmedetomidine; Tramadol; Preemptive analgesia; Osteoarthroplasty; Hemodynamics; Cognitive function

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前言

骨关节置换术是指膝关节或髋关节存在功能障碍的患者,通过使用人工关节进行代替,以重新获得较好的运动功能的一类手术方式^[1]。因手术本身会使大量炎性物质释放,致使机体中枢和外周神经系统痛觉敏感化,术后剧烈的疼痛不仅引发心、脑、肺等重要脏器的并发症,引起机体血流波动,还会对患者术后恢复造成影响^[2,3]。近年来,麻醉管理提出了"超前镇痛"这一概念,超前镇痛指在伤害性刺激作用于身体之前采取的一系列止痛措施,可防止中枢神经系统敏感化,进而减轻或消除术后疼痛^[4,5]。曲马多是非阿片类中枢性镇痛药,常用于各类外科手术的术后镇痛,可维持4~6h的镇痛作用^[6,7],但有研究显示大剂量的曲马多引起的不良反应较多,会降低患者的满意度及舒适度^[8]。右美托咪定是一种高选择性的 α_2 肾上腺素受体激动剂,可发挥较好的镇静、镇痛、抗交感效果^[9,10]。本研究通过对我院收治的部分骨关节置换术患者给予右美托咪定复合曲马多超前镇痛,取得了较好的效果,现作如下报道。

1 资料与方法

1.1 一般资料

选取2015年2月~2018年12月期间武警陕西省总队医院收治的行骨关节置换术患者121例,纳入标准:(1)均在我院择期行膝关节置换术或髋关节置换术者;(2)美国麻醉医师协会(ASA)^[11]分级I~II级;(3)无手术或麻醉禁忌症者;(4)均由同一组医师完成手术;(5)均对治疗方案知情并签署了同意书。排除标准:(1)既往有精神病史,无法配合完成本次研究者;(2)妊娠或哺乳期妇女;(3)合并心动过缓、心脏传导阻滞以及严重高血压者;(4)合并心肝肾等脏器功能不全者;(5)合并恶性肿瘤者。根据数表法将患者随机分为对照组($n=60$)和研究组($n=61$),其中对照组男32例,女28例,年龄39~62岁,平均(46.71 ± 2.94)岁;体质指数 $22.1 \sim 26.8 \text{ kg/m}^2$,平均(24.82 ± 0.73) kg/m^2 ;手术类型:膝关节置换术33例,髋关节置换术27例。研究组男35例,女26例,年龄37~64岁,平均(47.08 ± 3.98)岁;体质指数 $21.8 \sim 27.2 \text{ kg/m}^2$,平均(25.06 ± 0.69) kg/m^2 ;手术类型:膝关节置换术34例,髋关节置换术27例。两组患者基线资料比较无差异($P>0.05$),组间可比。本次研究已通过武警陕西省总队医院伦理委员会批准。

1.2 治疗方法

所有患者入院后行常规检查,择期行骨关节置换术。术前常规禁饮禁食,入室后建立静脉通道,采用长沙威胜电子有限公司生产的多功能监测仪监测患者心率(Heart rate, HR)、血氧

饱和度(Blood oxygen saturation, SPO_2)、呼气末二氧化碳分压(Pressure of end-tidal carbon dioxide, PETCO_2)、脑电双频指数(Bispectral Index, BIS)、平均动脉压(Mean arterial pressure, MAP)等生命体征指标,对照组于麻醉诱导前30min给予盐酸曲马多[福安药业集团湖北人民制药有限公司,国药准字H20060215,规格:0.1g(以盐酸曲马多计)]100mg,研究组于麻醉诱导前30min给予盐酸曲马多100mg联合右美托咪定[宜昌人福药业有限责任公司,国药准字H20183390,规格:2mL:200 μg (按右美托咪定计)]0.5 $\mu\text{g}/\text{kg}$ 。麻醉方法为喉罩插管静吸复合全身麻醉,两组麻醉诱导药物:依次注入咪达唑仑0.1mg/kg,舒芬太尼0.4 $\mu\text{g}/\text{kg}$,丙泊酚1mg/kg,顺苯阿曲库铵0.2mg/kg,术中喉罩吸入1%~2%七氟烷,麻醉维持药物:丙泊酚3mg/kg·h、瑞芬太尼0.4 $\mu\text{g}/\text{kg} \cdot \text{h}$,麻醉深度: $\text{PETCO}_2 < 45 \text{ mmHg}$,BIS值40~60。术中全程自主呼吸,若出现通气不足时给予呼吸机辅助通气。术后给予常规镇痛、抗感染处理。

1.3 观察指标

(1)于术前(T1)、术后4h(T2)、术后8h(T3)、术后12h(T4)、术后24h(T5)采用视觉模拟评分(Visual Analogue Scale, VAS)^[12]评价两组患者镇痛效果,其中VAS评分0~10分,其中0分表示无痛,10分表示难以忍受的疼痛,分数越高,其疼痛感越强烈。(2)记录两组患者T1~T5时间点的HR、MAP、 SPO_2 。(3)于术前、术后3d、术后1周采用简易精神状态量表(Simple Mental State Scale, MMSE)^[13]对两组患者认知功能进行评价,其中MMSE包括记忆力、定向力、回忆能力、注意力、语言能力以及计算力,总分30分,分数越高,认知功能越好。于术前、术后3d、术后1周抽取患者清晨空腹肘静脉血4mL,2900r/min离心12min,离心半径8cm,分离上清液,置于 -40°C 冰箱中待测。采用酶联免疫吸附试验检测中枢神经特异蛋白(Central nervous specific protein, S100 β)水平,严格遵守试剂盒(武汉博士德生物工程有限公司)说明书进行操作。(4)记录两组手术期间不良反应。

1.4 统计学方法

采用SPSS21.0统计学软件对数据进行统计学处理,计数资料以率的形式表示,采用 χ^2 检验,计量资料以($\bar{x} \pm s$)的形式表示,采用t检验,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组患者镇痛效果比较

两组患者T1时间点VAS评分比较无差异($P>0.05$);两组患者T2~T5时间点VAS评分呈先升高后降低趋势($P<0.05$);研究组T2~T5时间点VAS评分低于对照组($P<0.05$);详见表1。

表1 两组患者镇痛效果比较($\bar{x} \pm s$,分)

Table 1 Comparison of analgesic effect between two groups($\bar{x} \pm s$, scores)

Groups	T1	T2	T3	T4	T5
Control group($n=60$)	2.43 \pm 0.32	6.35 \pm 0.84 ^a	7.18 \pm 1.05 ^{ab}	5.02 \pm 0.66 ^{abc}	4.28 \pm 0.65 ^{abcd}
Research group($n=61$)	2.39 \pm 0.35	5.09 \pm 0.62 ^a	5.61 \pm 0.84 ^{ab}	4.31 \pm 0.79 ^{abc}	3.52 \pm 0.62 ^{abcd}
t	0.656	9.398	9.090	5.361	6.582
P	0.513	0.000	0.000	0.000	0.000

Note: Compared with T1, ^a $P<0.05$; compared with T2, ^b $P<0.05$; compared with T3, ^c $P<0.05$; compared with T4, ^d $P<0.05$

2.2 两组患者血流动力学指标比较

两组患者 T1 时间点 HR、SPO₂、MAP 比较差异无统计学意义 ($P>0.05$); 研究组 T2~T5 时间点 HR、SPO₂、MAP 与 T1 时间点比较差异无统计学意义 ($P>0.05$); 对照组 T2~T5 时间点

HR、MAP 较 T1 时间点升高, SPO₂ 较 T1 时间点下降 ($P<0.05$); 研究组 T2~T5 时间点 HR、MAP 低于对照组, SPO₂ 则高于对照组 ($P<0.05$); 详见表 2。

表 2 两组患者血流动力学指标比较($\bar{x} \pm s$)

Table 2 Comparison of hemodynamic indexes between two groups($\bar{x} \pm s$)

Groups	Time point	HR(beats/min)	MAP(mmHg)	SPO ₂ (%)
Control group(n=60)	T1	82.07± 9.22	113.68± 8.34	98.77± 10.52
	T2	85.29± 10.26 ^a	118.93± 10.45 ^a	93.47± 11.48 ^a
	T3	87.59± 11.37 ^a	117.37± 9.54 ^a	92.55± 9.31 ^a
	T4	88.83± 9.49 ^a	116.56± 9.61 ^a	92.07± 10.22 ^a
	T5	89.23± 10.51 ^a	118.69± 10.37 ^a	93.53± 8.43 ^a
Research group(n=61)	T1	82.97± 10.37	113.84± 8.27	98.32± 10.22
	T2	83.39± 11.25 ^b	112.95± 11.35 ^b	97.31± 12.25 ^b
	T3	81.67± 9.22 ^b	111.23± 9.39 ^b	96.25± 11.36 ^b
	T4	80.90± 9.42 ^b	112.39± 9.62 ^b	97.85± 10.12 ^b
	T5	83.21± 10.25 ^b	114.56± 10.48 ^b	98.93± 9.09 ^b

Note: Compared with T1, ^a $P<0.05$; compared with control group, ^b $P<0.05$.

2.3 两组患者认知功能比较

两组患者术前 MMSE 评分、S100β 水平比较差异无统计学意义 ($P>0.05$); 对照组患者术后 3 d、术后 1 周 MMSE 评分呈先降低后升高趋势, S100β 呈先升高后降低趋势 ($P<0.05$);

研究组术后 3 d MMSE 评分低于术前, S100β 则高于术前 ($P<0.05$); 研究组术后 3 d、术后 1 周 MMSE 评分高于对照组, S100β 则低于对照组 ($P<0.05$); 详见表 3。

表 3 两组患者认知功能比较($\bar{x} \pm s$)

Table 3 Comparison of cognitive function between two groups($\bar{x} \pm s$)

Groups	MMSE(scores)			S100β(μg/L)		
	Preoperative	3 d after operation	1 week after operation	Preoperative	3 d after operation	1 week after operation
Control group (n=60)	28.17± 1.15	23.85± 1.31 ^a	26.09± 1.04 ^{ab}	0.05± 0.02	0.18± 0.05 ^a	0.10± 0.02 ^{ab}
Research group (n=61)	28.23± 1.04	27.24± 1.27 ^a	28.17± 1.13	0.05± 0.01	0.11± 0.03 ^a	0.06± 0.01
t	0.301	14.453	10.531	0.000	9.356	13.949
P	0.764	0.000	0.000	1.000	0.000	0.000

Note: Compared with preoperative, ^a $P<0.05$; compared with 3 d after operation, ^b $P<0.05$

2.4 两组患者不良反应发生情况

两组不良反应总发生率比较无差异 ($P>0.05$), 详见表 4。

表 4 两组不良反应发生情况的比较 [n(%)]

Table 4 Comparison of adverse reactions between the two groups [n(%)]

Groups	Nausea	Dizzy	Respiratory depression	Hypotension	Bradycardia	Total incidence
Control group(n=60)	4(6.67)	6(10.00)	2(3.33)	2(3.33)	2(3.33)	16(26.67)
Research group(n=61)	6(9.84)	7(11.48)	3(4.92)	2(3.28)	3(4.92)	21(34.43)
χ^2						0.977
P						0.323

3 讨论

疼痛已成为继体温、血压、脉搏、呼吸之后的第五大生命体征,而骨关节置换术后致痛物质的大量释放,可对人体产生双向损害作用,一是手术期间,对机体组织创伤所产生的伤害性感受,可引起机体血流动力学波动;二是术后疼痛会影响患者的术后锻炼,进而导致局部肌力降低,关节置换效果变差^[14-16]。由此可见,围术期良好的镇痛效果是确保手术顺利实施的前提。此外,既往有研究报道骨科术后患者认知功能障碍的发生率已达5.1%~61%,可影响患者预后^[17]。超前镇痛概念起源于20世纪初,于麻醉诱导前给予患者超前镇痛,可防止外周损伤冲动向中枢神经系统传递,是一种较为有效的镇痛方法^[18]。曲马多是一种中枢性镇痛药物,对阿片类受体中的 μ 受体有较弱的亲和力,主要通过抑制神经元突触对去甲肾上腺素的再摄取而影响痛觉传递,产生镇痛效果^[19,20],但不少研究^[21,22]证实麻醉管理中曲马多镇痛剂量过少时,达不到镇痛效果;剂量过大时,又易引起眩晕、呕吐及恶心等不良反应。右美托咪定是临床常用于各类辅助麻醉和围术期镇痛的麻醉药物,主要通过作用于蓝斑、脊髓内的 α_2 受体,产生镇静、镇痛作用。

本次研究结果显示,研究组术后不同时间点VAS评分均低于对照组,提示右美托咪定复合曲马多超前镇痛可发挥较好的镇痛效果。分析其原因,术前使用曲马多,可降低中枢兴奋性,减少手术时的中枢致敏,使伤害性刺激无法传递,同时还可防止术后一段时间内的中枢神经致敏化的形成,达到超前镇痛的效果^[23,24]。右美托咪定可激活中枢突触后膜上的 α_2 肾上腺素受体,进而增强抑制性神经元兴奋,减少交感活动传出,同时还可激动脊髓后角的 α_2 肾上腺素受体,从而抑制感觉神经递质释放,提高机体对疼痛的阈值^[25,26]。右美托咪定、曲马多通过作用于疼痛机制的不同环节,发挥协同镇痛效果。本次研究结果还显示,对照组患者存在一定的血流波动,而右美托咪定复合曲马多超前镇痛患者血流波动不明显。这可能是因为右美托咪定可对去甲肾上腺素的释放进行抑制,进而缓解患者因疼痛所致的HR、MAP波动,同时右美托咪定还可调控机体交感神经活性,进而维持血流动力学平稳^[27,28]。S100 β 蛋白是一种局部缺血性脑损伤的血清标记物,研究组S100 β 水平低于对照组,且研究组术后MMSE评分高于对照组,提示右美托咪定复合曲马多超前镇痛对患者认知功能影响较轻,右美托咪定对中枢神经系统有一定的保护作用。容雄飞等人^[29]动物实验证实,在麻醉后脑缺血的老鼠模型病理切片中,使用右美托咪定可明显改善小鼠脑缺血现象。两组不良反应发生率比较无差异,而李晓兰等人^[30]研究却认为,右美托咪定复合曲马多超前镇痛可减少不良反应发生率,差异有统计学意义。这与本次研究结果不一致,可能是纳入病例存在个体差异所致。后续研究将扩大样本量、严格制定筛选标准,以获取更为准确的数据。

综上所述,骨关节置换术患者给予右美托咪定复合曲马多超前镇痛,可有效维持血流动力学稳定,且对机体认知功能影响较轻,镇痛效果确切,安全性较好,临床应用价值较高。

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